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THE OPERATIVE LENGTHENING OF THE TIBIA AND FIBULA*

A PRELIMINARY REPORT ON THE FURTHER DEVELOPMENT OF THE PRINCIPLES AND TECHNIC

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IN 1924, at the Shriner's Hospital for Crippled Children in St. Louis, we performed our first operation for lengthening the tibia and fibula in a patient in whom shortening of one leg had followed an attack of acute anterior poliomyelitis. In this patient, a gain in length of one and one-half inches was secured together with a decided functional improvement. Encouraged by this result, we decided to use the operation in a selected group of cases where shortening of one of the lower extremities constituted the major disability. A description of the procedure and the results obtained in the first six patients was published in January, 1927.[1]

Further experience led to improvement in the technic of operation and to further development of apparatus and, by 1930, we had operated upon 73 patients, 48 of whom had lengthening of the tibia and fibula and 25 of whom had lengthening of the femur. The results obtained and the difficulties and complications encountered were discussed in further publications.[2, 3, 4]

Our work stimulated an increasing interest in bone lengthening operations at various clinics in this country. The literature reflects this interest, since a substantial number of operations, with satisfactory results, have now been reported. Brockway,[5] in reviewing a series of 46 leg lengthenings, states: "When the operation for the lengthening of legs was first presented to the profession, it was believed by many to be a very formidable procedure involving considerable risk. Tested by actual experience, the operation has been found to be most practical and safe." Other surgeons have reported their results in a considerable group of cases. All of them, however, have recorded complications. While in some instances these complications might have been caused by inexperience with the details of the procedure, we know that these

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complications will occur even in the hands of experienced surgeons who are thoroughly conversant with the operation. We can only attribute these complications to imperfections in the method which we have outlined in our previous publications.

These complications have led to a gradual loss of interest in the procedure of leg lengthening, and other less radical operations have been substituted. Shortening of the sound leg by fusion of the epiphyses at the knee, at the ankle, or both, has been developed in a highly scientific manner by Phemister.[6] Resection of a segment of the femur or osteotomy of the femur with overlapping and fixation of the fragments by pins, has been practiced extensively by White.[7] The excellent work of these surgeons has placed leg shortening on a sound basis. While leg shortening is not always free from complications, it is a much simpler undertaking than leg lengthening. It is our opinion, therefore, that, in the present stage of development of this operation, for the majority of patients with shortening of one of the lower extremities, the operation of leg shortening by the method of White or the epiphyseal arrest, as practiced by Phemister, is preferable to leg lengthening. There are certain patients, however, in whom epiphyseal arrest is no longer applicable because they have reached maturity. There are others of short stature in whom further reduction in height is undesirable and especially in patients with a marked degree of shortening; furthermore, it is to be borne in mind that leg shortening is carried out on the sound limb and on this ground may be objected to by the patient. Such indications for leg lengthening make it desirable to retain the procedure for a limited group and, in consequence, we have conducted further studies with a view to reducing the chances of complications. The results of these studies point to a clearer recognition of certain fundamental principles for the technic of operation. Our experience with the new technic has not been sufficiently extensive to merit any final conclusions, but we feel that our results should be recorded. This present communication is entirely in the nature of a preliminary report.

The Complications of Leg Lengthening.—We believe a list of the common complications of leg lengthening is an essential preliminary to a discussion of methods:

(I) Deformities of the foot: (a) Valgus, (b) Equinus, (c) Equinovalgus, (d) Calcaneovalgus.

(II) Deformities of the knee: (a) Genuvalgum, (b) Flexion contracture, (c) Relaxation of the knee.

(III) Anterior and medial bowing of the fragments of the tibia with mal- or nonunion.

(IV) Limitation of motion at the ankle.

(V) Weakening of the muscles of the leg.

(VI) Nerve complications: (a) Paralysis or weakening of the muscles, (b) Disturbance of sensation.

(VII) Disturbance of circulation (chronic swelling of the leg).

(VIII) Infection: (a) Infection of the operative wound, (b) Infection of pin wounds.

(IX) Aseptic necrosis of bone (Compere[8]).

The deformities of the foot, of the knee and the bowing of the fragments of the tibia, with consequent malalignment or nonunion, are caused by the failure of the soft parts to lengthen proportionately with the bones. The soft parts of major significance are the deep fascia, the intermuscular septa, the interosseous membrane and the periosteum. In addition, the tendinous content of the muscles offer great resistance to lengthening. For the most part, these fibrous structures are more intimately blended with the fibula than with the tibia; therefore, the segments of the fibula do not separate equally with those of the tibia.

At the ankle, the internal malleolus moves distally, while the external malleolus remains relatively fixed in position with not only subluxation at the lower tibiofibular joint but also alteration of the mortice of the ankle joint itself. The change in the mortice and the resistance of the peroneal muscles and of the ligaments passing from the external malleolus to the os calcis and astragalus, force the foot into valgus. This position may be converted into equinovalgus or calcaneovalgus, depending upon the relative resistance of the dorsal and plantar flexors of the foot.

On the lateral side of the knee, the deep fascia and the intermuscular septa blend intimately with the lateral ligaments and the capsule of the knee joint, the biceps femoris tendon and the iliotibial tract. The tension developed in these structures during the lengthening forces the knee into flexion and adduction. Stretching of the internal lateral ligament follows with resultant genuvalgum and instability of the joint. Occasionally the head of the fibula may separate from the tibia and move downward. This displacement has not been of great consequence yet it may stretch the external lateral ligament and cause further relaxation of the knee.

We believe limitation of motion at the ankle is caused by a traumatic arthritis which is due to the tremendous pressure on the articular surfaces of the joint. Where there is also malalignment of the joint, this arthritis may become progressive in character.

In our experience, injuries to the nerves, with partial paralysis of the muscles, disturbance of sensation and interference with circulation, have not been frequent or serious complications. These are undoubtedly the outcome of overstretch during lengthening.

In a procedure of such magnitude, which requires wide opening of the medullary canal, infection of the operative wound may readily occur unless the strictest attention is paid to asepsis and to the gentleness with which the tissues are handled. Pressure necrosis of the skin and soft tissues, with attendant osteomyelitis, is due to the lack of complete control of the fragments. Infection of the pin wounds is caused by trauma during their insertion, by pressure necrosis of the soft tissues and bone and also by too frequent changes of dressings. It is our experience that the dressings should not be changed unless there is absolute necessity for it. An unrecognized, but none the less

important, factor in the production of osteomyelitis is the migration of pins from side to side. Undue irritation from faulty metal used in the construction of the pins is another important cause of bone destruction. We agree with the conclusions of Compere,[8] in that aseptic necrosis of the fragments may result from too extensive stripping of the periosteum. In the presence of infection, this aseptic necrosis may change to septic necrosis, and resultant osteomyelitis with all its disastrous sequelae.

The weakness of the muscles, apart from nerve injury, may be attributed to overstretching of their fibers beyond the limits of their elasticity.

Discussion of the Principles of Leg Lengthening.—In early publications, we stressed the importance of the application of certain fundamental principles in order to lengthen a bone, which were: First, traction must be made directly on the bone itself; second, in order to overcome the elastic resistance of the soft parts, traction must be slow and continuous in type; and third, to avoid harmful pressure on these soft parts, alignment and contact of the fragments must be maintained during the lengthening process. Further experience with the procedure has convinced us that with the operation, as performed even with the four-pin control, the application of the third principle is difficult of attainment. We early recognized that an important cause of malalignment was the resistance of the fibrous structures, particularly those attached to the fibula. We, therefore, advised and carried out increasingly radical divisions of the deep fascia, the intermuscular septa, the periosteum and the interosseous membrane. A just criticism was offered by Haboush and Finkelstein,[9] on the ground that the division of these structures was at an incorrect level. We had already realized this at the time and further studies emphasized it.

In the course of our studies we carried out many anatomic dissections of the leg. Our purpose was: First, to determine the exact anatomic relation of the deep fascial envelope, the intermuscular septa and the interosseous membrane to the tibia and fibula. Second, we wished to satisfy ourselves as to the exact relation of the muscles of the leg to these fibrous structures and to the bone. These dissections disclosed that no matter how radical the division of the fascial envelope, the intermuscular septa, the interosseous membrane and the periosteum, considerable resistance was still offered to lengthening. This resistance was due to the enormous fibrous content of the muscle bellies. A fact not fully appreciated, is that in any muscle the fleshy part contains an amount of fibrous tissue equal to the bulk of its tendon. The tendon of a muscle passes from its origin to its insertion, being only expanded in its muscular substance. Because of this arrangement, complete division of the fibrous parts, *etc.,* leaves a large part of the resistant fibrous elements untouched. When a muscle is stretched beyond its inherent elasticity it can only yield at the expense of its passive elements. Destruction and breaking down of these elements leads to permanent damage with scar formation in the muscle substance. We regard the loss of muscular power as due, not only to overstretch, but also to contractures in the muscles. This is evidenced by the progressive development of fixed deformity, not infrequently met with in leg lengthening.

It is evident, therefore, that the prevention of overstretch of the muscles demands either lengthening of their tendons at the ankle or the freeing of their origins from the upper parts of the tibia and fibula. Multiple tendon lengthening is impractical and would produce a widespread weakness of the muscles which would defeat our purpose. The only alternative, therefore, was to consider the practicability of freeing the origin of the muscles sufficiently to permit the performance of such osteotomies as would allow bodily migrations of these muscles with the descending fragments of the bones. To determine whether or not this plan was feasible, we carried out anatomic dissections.

Anatomic Considerations.—In these dissections we were primarily concerned with the following structures: (A) The deep fascia, (B) The interosseous membrane, (C) The origin of the muscles, (D) The points of fixation of the blood vessels and the nerves, (E) The nutrient vessels.

(A) *The Deep Fascia.*—This forms a complete envelope for the leg except over the subcutaneous surface of the tibia and over a small triangular area about the lateral malleolus of the fibula. In these regions it is continuous with the periosteum of these two bones. Proximally, it blends with the fascia lata and is strengthened by expansions from the tendons about the knee. The fascia is notably dense over the anterolateral aspect of the leg where its deep surface gives partial origin to the extensor and peroneal musculature. Distally, it presents additional fibers which constitute the series of retinacula which bind the tendons in the region of the ankle and the foot.

On the anterolateral aspect of the leg two intermuscular septa, the anterior and posterior peroneal septa, pass from the deep fascia to the fibula. The anterior peroneal septum encloses the superficial peroneal nerve and separates the extensor from the peroneal muscles. The posterior peroneal septum separates the peroneal muscles from the muscles of the calf. These septa are expanded and especially thick where they blend with the deep fascia and they divide the leg into three osteofascial compartments—an anterior, a lateral and a posterior or flexor compartment. There are several other subsidiary septa. One of these extends from the posterior peroneal septum across the posterior compartment of the leg on the surface of the deep flexor muscles to meet the tibia. It encloses the posterior tibial vessels and nerves and is best defined in the distal two-thirds of the leg. Another fairly strong sheet of fascia covers the tibialis posterior muscle and separates it from the flexors of the toes. This fascial septum is continuous with the fascia on the surface of the popliteus muscle where it is strengthened by an expansion from the tendon of the semimembranosus. In the anterior compartment there are a series of weak and ill defined septa separating the individual extensor muscles.

(B) *The Interosseous Membrane.*—The interosseous membrane occupies the interval between the two bones. Above, it has a large aperture for passage of the anterior tibial vessels; below, a similar one for the passage of the perforating peroneal artery. Posteriorly, it gives partial origin to the tibialis posterior muscle while, anteriorly, it is directly related, in the proximal two-thirds of the leg, to the anterior tibial vessels.

(C) *The Origin of the Muscles.*—The origins of the muscles are given in the following tabulated form (Table I).

TABLE I

MUSCLES OF THE ANTERIOR COMPARTMENT

Tibialis Anterior	*Extensor Digitorum Longus*	*Extensor Hallucis*
Lateral condyle tibia	Proximal two-thirds anterior half of medial surface of fibula	Intermediate two-thirds anterior half of medial surface of fibula
Proximal two-thirds lateral surface of tibia	Interosseous membrane	Interosseous membrane
Interosseous membrane	Neighboring septa	Neighboring septa
Overlying deep fascia	Overlying fascia	
Septum between it and extensor digitorum longus		

Peroneus Tertius

Distal one-third of the anterior half of the medial surface of fibula
Interosseous membrane
Neighboring septa

MUSCLES OF THE LATERAL COMPARTMENT

Peroneus Longus	*Peroneus Brevis*
Head and proximal two-thirds of the lateral surface of fibula	Distal two-thirds of the lateral surface of fibula
Intermuscular septa	Intermuscular septa
Overlying fascia	

MUSCLES OF THE POSTERIOR COMPARTMENT

Gastrocnemius	*Soleus*
Lateral head	Head and proximal one-third of posterior surface of fibula
Distal part of lateral epicondylar line of femur and lateral surface of condyle	Fibrous arch over popliteal vessels
Medial head	Oblique popliteal line
Medial side of popliteal surface of femur	Intermediate one-third of medial border of tibia

DEEP GROUP

Popliteus (insertion)	*Flexor Digitorum Longus*	*Flexor Hallucis Longus*
Popliteal line and triangular surface above it	Intermediate three-fifths posterior surface of tibia, medial to vertical line	Distal two-thirds posterior surface of fibula
	Fascia on surface of tibialis posterior	Fascia over tibialis posterior
		Interosseous membrane
		Posterior intermuscular septum

Tibialis Posterior

Posterior half of the medial surface of fibula
Proximal two-thirds of the posterior surface of tibia, lateral to vertical line
Lateral condyle
Interosseous membrane
Fascia covering it

(D) *Points of Fixation of the Vessels and Nerves.*—The vessels and nerves of the leg present very definite points of fixation. The common peroneal nerve passes from undercover of the tendon of the biceps femoris muscle to

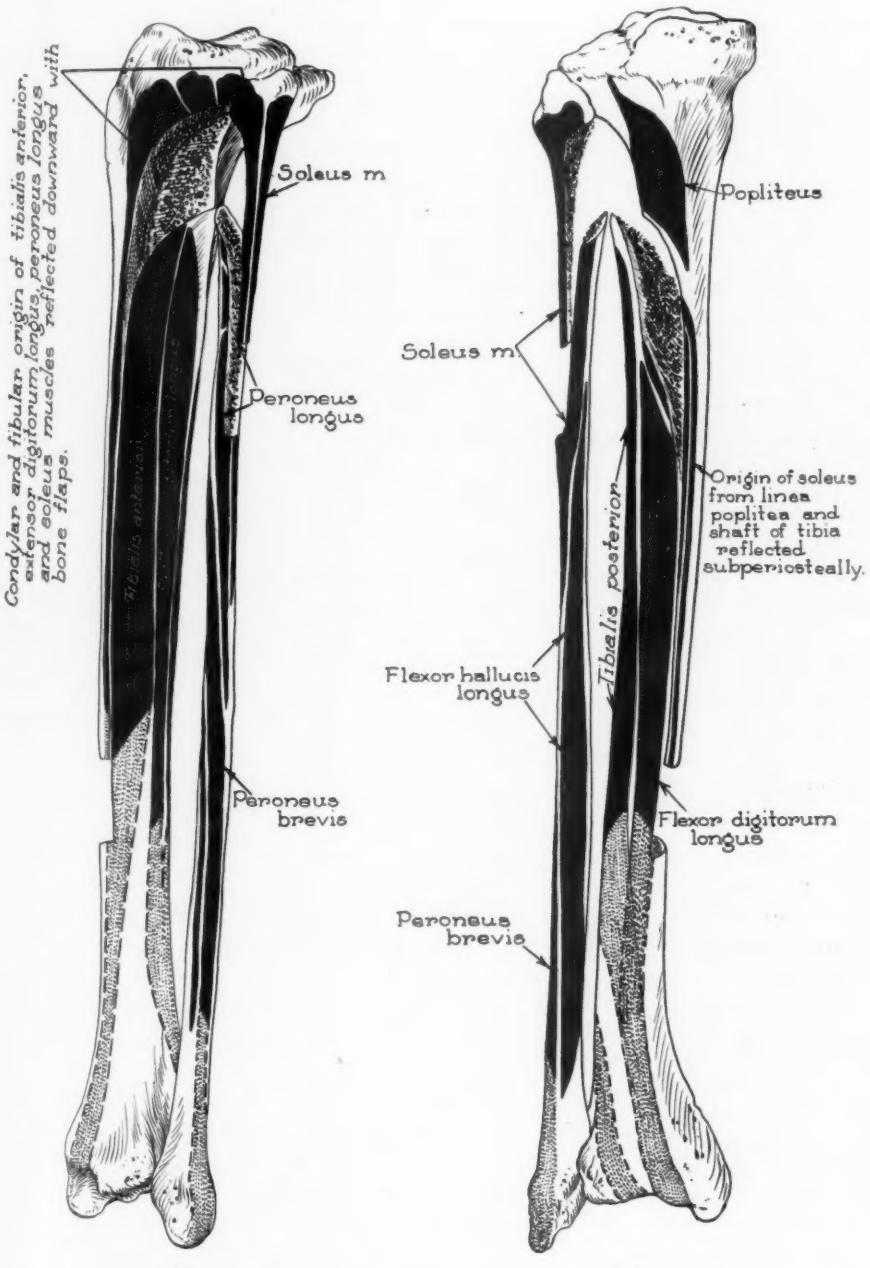
Condylar and tibular origin of tibialis anterior, extensor digitorum longus, peroneus longus and soleus muscles reflected downward with bone flaps.
Soleus m
Peroneus longus
Peroneus brevis
Popliteus
Soleus m
Origin of soleus from linea poplitea and shaft of tibia reflected subperiosteally.
Tibialis posterior
Flexor hallucis longus
Flexor digitorum longus
Peroneus brevis
(A)
(B)

FIG. 1 (A and B).—The origin of the muscles from the anterior and posterior surfaces of the tibia and fibula with osteotomies of both bones in the anteroposterior plane to permit bodily migration of the origin of the muscles with the descending fragments.

pierce the fascial envelope of the leg. It winds around the neck of the fibula and into the lateral compartment in front of the posterior peroneal septum. Just prior to piercing the fascial envelope, it is held in place by a fibrous expansion from the tendon of the biceps. The popliteal vessels are fixed at two points. The first point of fixation is where its anterior tibial division passes through the interosseous membrane; the second is where the posterior tibial artery passes beneath the arch of the soleus.

(E) *Nutrient Vessels.*—The nutrient artery to the tibia is usually given off from the posterior tibial artery just below the fibrous arch of the soleus. It passes medially and downward undercover of the soleus to pierce the substance of the flexor digitorum longus and enters the bone. This vessel gives off several muscular branches, one of which is found entering the soleus muscle at about the level of the oblique popliteal line. The nutrient artery to the fibula is a branch of the peroneal artery. It may enter the bone at the junction of its upper and middle thirds or at its lower and middle thirds.

The anatomic arrangement may be summarized by recognizing that the muscles passing from the tibia and fibula to the foot arise from a bony and fibrous Gothic arch with lateral pillars consisting of the shafts of the two bones (Fig. 1 a and b). The outer fibular pillar is completely invested with muscles and its surfaces for attachment are extended by the intermuscular septa. The inner tibial pillar gives origin to muscles except for its medial subcutaneous surface. The interval between the pillars is occupied by the interosseous membrane which affords additional surfaces for the origin of muscles. The deep fascia invests the leg circumferentially with the exception of the medial surface of the tibia. In the region of the apex of the arch it gives origin to the muscles on the anterolateral aspect of the leg.

With this arrangement in mind, we considered a procedure for freeing these muscles by a complete subperiosteal reflection from the upper parts of the tibia and fibula. The magnitude of the periosteal reflection necessary to accomplish this would deprive large segments of both bones of a large part of their blood supply. In addition, this procedure, necessarily blind, would endanger the important blood vessels and nerves in the vicinity. This method was, therefore, not adopted and, later, we decided that these important structures could be better exposed by two incisions, one, on the anterolateral and the other on the posteromedial aspects of the lower thigh and upper leg.

The following cases illustrate the practical application of these new principles. All of these operations were performed with a tourniquet applied.

Case 1.—E. G., male, age 13. Admitted, March 10, 1936.

Chief Complaint.—Shortening of the right leg.

Present Illness.—Acute anterior poliomyelitis at the age of six, with residual paralysis of the right leg.

Physical Examination.—Marked atrophy of the muscles of the right leg. The muscles which showed moderate power were the gastrocnemius, the peroneus longus and brevis. The foot was in equinovalgus. There were two inches of shortening.

Operation, March 19, 1936.—The operation was performed as a single stage procedure. The upper attachment of the muscles, the popliteal and tibial vessels, and the

peroneal and tibial nerves were exposed through anterolateral and posteromedial incisions. The origin of the peroneus longus, the soleus, the extensor digitorum longus and the tibialis anterior muscles were freed subperiosteally from the upper ends of the tibia and fibula in the region of the arch formed by these two bones. The intermuscular septa, the interosseous membrane and the deep fascia were divided. The fibula was osteotomized by an oblique section of its upper end. The tibia was divided by a transverse cut through the posterior cortex just below the level of the linea poplitea. The extremities of this division were joined by linear sections of the cortex, three inches in length, on the middle of the medial and lateral surfaces of the tibia. The four-pin apparatus was applied and the osteotomy was completed by a cross-cut of the anterior crest of this bone, uniting the linear sections on either side.

Postoperative Notes.—An infection developed about the upper pins, from which a quantity of pus discharged for several days. The temperature subsided gradually and the wound closed. Despite the infection, lengthening was continued and the desired two inches was obtained.

Final Result.—Union with satisfactory alignment, two inches gain in length and excellent improvement in function. The slight equinus deformity present before lengthening was subsequently corrected by stabilization of the foot.

COMMENT.—The lessons we learned from our experience with this patient were that the operation was entirely too extensive for one stage, and that the periosteal stripping was excessive. These difficulties were no doubt related to the infection of the pin wounds and the development of a mild localized osteomyelitis.

In our next case, we decided to perform the operation in two stages, and we also planned an osteotomy of the tibia which would reduce the amount of periosteal stripping.

Case 2.—B. W., female, age 13. Admitted, November 10, 1936.

Chief Complaint.—Shortening of the right leg.

History.—At the age of 13 months, this patient had acute anterior poliomyelitis, which was followed by paralysis of the right leg. At the age of 10, she had a stabilization of the right foot.

Physical Examination.—There was no power demonstrable in the muscles on the posterior aspect of the leg. The dorsal flexors of the foot and the extensors of the toes were strong. There were two and one-half inches of shortening of the right lower extremity, two inches of which were confined to the leg.

Operation, November 13, 1936.—As in Case 1, the muscular attachments, the vessels and bones were exposed through two incisions. The muscles were detached in essentially the same manner as in Case 1 except that the periosteal stripping was less extensive on the posterior aspect of the tibia. The fascia, the intermuscular septa and the interosseous membrane were freely incised and the fibula was obliquely transected at its upper end. The beginning of an oblique osteotomy, which was contemplated for the second stage, was commenced on the posterior aspect of the tibia at the lower end of the linea poplitea. From this site it was continued forward and downward for approximately one inch.

Second Stage Operation.—November 25, 1936: The four-pin apparatus was applied. The posteromedial incision of the first stage was continued forward and downward onto the crest of the tibia. The periosteum was stripped from the anterior half of the tibia for a distance of three inches and the oblique osteotomy of this bone was completed. A half inch of lengthening was obtained.

Postoperative Notes.—Lengthening was begun December 2, 1936, seven days after the completion of the second stage. By December 13, lengthening was increased two

inches, which means that one and one-half inches had been gained in 11 days. It was noted that the fragments of the tibia tilted forward, and that this was reduced by flexion of the knee. There was some persistence, however, of this tilting which prevented contact of the two fragments distally.

Final Result.—At the present time, one year and 10 months after operation, union of the fragments has taken place only at their upper halves.

COMMENT.—The inferior extremity of the upper fragment failed to unite solidly to the lower fragment because of the separation of the fragments and of the extensive stripping of the periosteum from the lower end of the upper fragment.

The patient is now walking with a caliper brace and she has good function. There have been no complications of knee or foot, no internal bowing of

FIG. 2 (A, B, and C).—Case 3: Two and one-half inches of shortening of the tibia and fibula and four inches of shortening of the femur. Total shortening of six and one-half inches. Note closure of lower femoral and upper tibial epiphyseal lines with compensatory bowing of the fibula. Calcaneous deformity of the foot.

the tibia and no indication of injury to the blood vessels or nerves. A tendon transplant on the foot together with a minor bone grafting operation will free this patient from apparatus.

Case 3.—W. M., male, age 13. Admitted, September 13, 1936. Referred by Dr. Harold H. Hitchcock, of Oakland.

Chief Complaint.—Progressive shortening of the left leg over a period of 11 years.

History.—At the age of two, the patient had tuberculosis of the left hip. He was treated conservatively until the age of nine, when an arthrodesis of the hip was performed. Following this, he sustained two fractures of the left tibia in the region of the knee, and he was supposed to have had an attack of acute anterior poliomyelitis affecting the left leg, time of onset unknown.

Physical Examination.—The patient walks with crutches. His left hip is fixed in 40° of flexion, neutral as regards abduction, adduction and rotation. There is a marked atrophy of the bones and muscles of this extremity and there is a calcaneous deformity of the foot. The measurements showed six and one-half inches of actual shortening of the left lower extremity, four inches in the thigh and two and one-half inches in the leg. The roentgenograms showed incomplete fusion of the left hip, marked shortening

of the extremity and obliteration of the lower femoral and upper tibial epiphyseal lines. There was a marked internal bowing of the tibia and a compensatory bowing of the fibula so that its middle portion was displaced behind the tibia (Fig. 2 a, b and c).

Operations, December 15, and December 22, 1936.—These were carried out in two stages. In the first stage, the approach used was the same as that employed in Case 2. At this time the fibula was sectioned obliquely together with freeing of the fibrous structures. At the second stage, the four-pin apparatus was applied and the tibia was osteotomized in a Z-shaped manner, as in Case 1, through an extension of the posteromedial incision. A half-inch gain was obtained.

Postoperative Notes.—Lengthening was carried out for three weeks after completion of the second stage, when an increasing equinus rendered subcutaneous tenotomy of the tendo achillis necessary. Lengthening was then continued and, at the end of 48 days, three inches had been gained. There was good alignment and considerable formation of callus (Fig. 3 a and b).

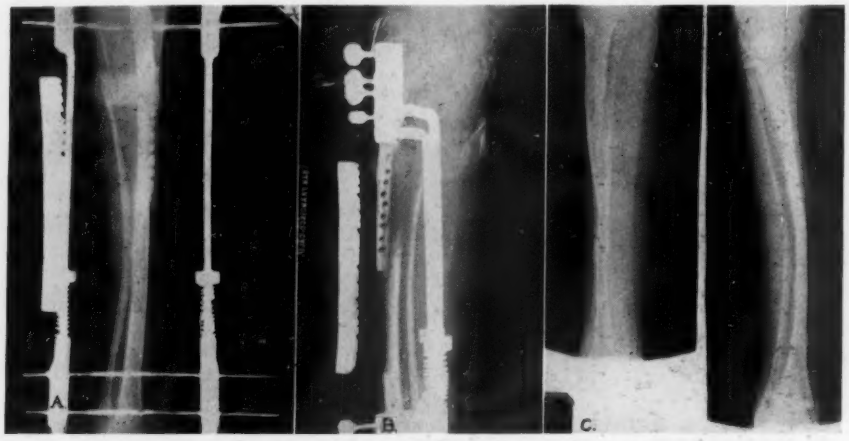

FIG. 3 (A and B).—Case 3: Anteroposterior and lateral views, 48 days postoperative, showing three inches gain in length with good alignment and beginning formation of callus. (C)—Seven months after operation with restoration of the medullary canal of the tibia.

Subsequent Course.—April 17, 1937: (Approximately seven months after operation.) Roentgenograms show satisfactory length and alignment with union and restoration of the medullary canal (Fig. 3 c).

May 4, 1937.—The patient was readmitted. He is now 14 years of age. On this day, he slipped and fell, fracturing the femur at the upper margin of the plaster encasement which he was wearing for the protection of his osteotomized tibia and fibula.

Physical Examination.—There was considerable swelling, ecchymosis and crepitus at the site of fracture. Roentgenograms disclosed an irregular, transverse fracture at the middle third of the left femur. The following plan of treatment was carried out:

May 5, 1937.—A Hoke traction spica was applied with a special leg lengthening apparatus incorporated.

May 12, 1937.—Through an oblique incision, the tendons of the rectus and vastus intermedius muscles were freed down to their insertions at the patella. The rectus tendon was sectioned just above the patella and turned upward. The vastus lateralis and medialis were freed from the lateral aspects of the patella and from the intermedius tendon. The intermedius muscle was then sectioned at the junction of its tendon and belly. Tenotomy of the tendon adductor magnus at the level of the adductor tubercle and freeing of the tendon to the level of the lower part of Hunter's canal liberated the origin of the lower part of the vastus medialis. The rectus and intermedius tendons were sutured to each

other with plenty of slack. The insertions of the vastus lateralis and medialis were moved upward and sutured to the lateral margins of the intermedius and rectus tendons. The site of the fracture was exposed and the periosteum stripped from the ends of the upper and lower fragments.

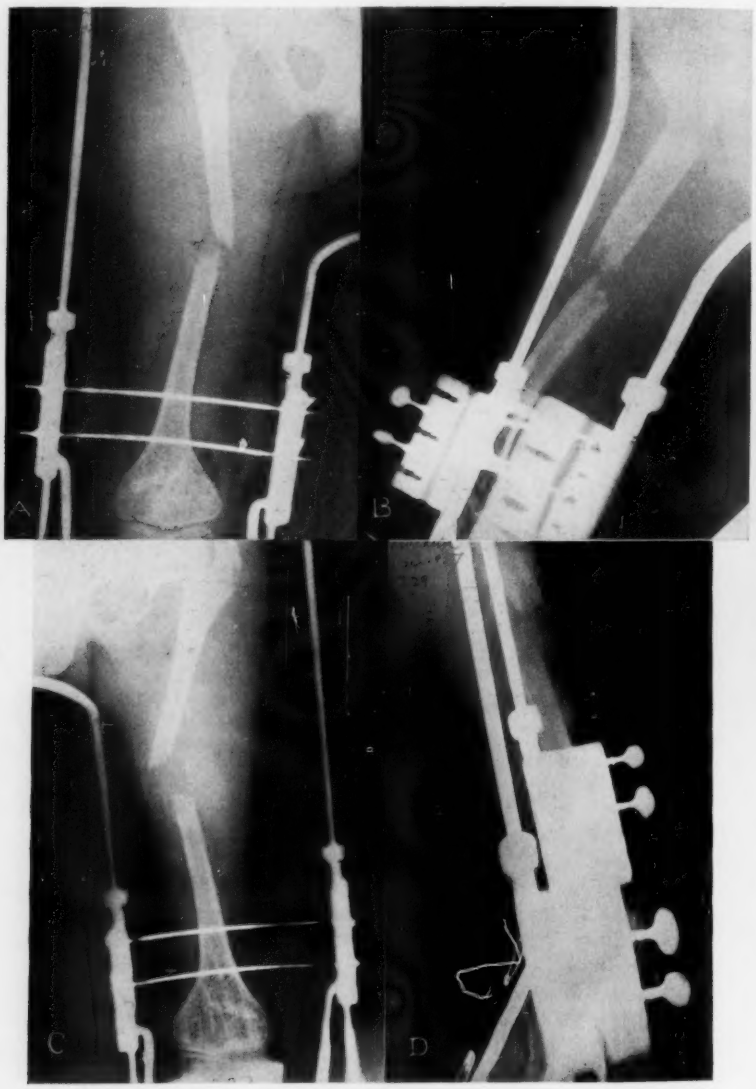

FIG. 4 (A and B).—Case 3: Anteroposterior and lateral views 14 days after fracture of the femur with apparatus applied for lengthening. (C and D)—Anteroposterior and lateral views, 20 days after fracture. Note extensive formation of callus.

May 18, 1937.—Under general anesthesia, two, one-eighth inch pins were passed horizontally through the lower end of the femur, tension was applied and one-half inch gain secured. Roentgenograms show traces of formation of callus (Fig. 4 a and b).

May 24, 1937.—Roentgenograms taken 20 days after fracture, and 12 days after operation, show increased formation of callus at the site of fracture (Fig. 4 c and d).

May 26, 1937.—Two oblique pins were drilled through the cortices of the upper fragment, the projecting ends of which were fastened to the lateral bars of the traction apparatus. This was done because the patient was rotating in his spica and there was insufficient counter traction.

June 10, 1937.—Roentgenograms showed massive formation of callus and two inches of lengthening.

July 19, 1937.—Two and one-third inches of lengthening.

September 30, 1937.—Additional formation of callus and an increase in the size of the shaft of the femur (Fig. 5 a and b). Total gain in length was five and one-third inches (Fig. 5 c). At this time the patient had two inches of shortening.

Final Result.—September 20, 1938: Due to the patient's having grown two inches during the past year, the measurements now show nearly three inches of shortening. We

FIG. 5 (A and B).—Case 3: Anteroposterior and lateral views five months after fracture showing extensive formation of callus with union. Gain in length of two and one-third inches. Total gain in length of extremity, five and one-third inches. (C)—Anteroposterior view eight months after fracture. Note correction of alignment by formation of callus on the outer aspect of the lower end of the upper fragment.

made a mistake of not effecting an arrestment of the lower femoral and upper tibial epiphyses of the normal side. A plaster of paris encasement has been worn since the last operation, which is now being changed to a brace.

COMMENT.—Our experience in this case raises a number of important points relative to formation of callus. This patient had six and one-half inches of shortening which increased to eight and one-half inches through further growth. By operative lengthening of the tibia, fibula and femur, five and one-third inches were gained. The formation of callus in the femur was unusually massive, and the question arises as to whether or not this might be the outcome of procedures carried out during a critical period of new formation of bone. It is interesting to observe that there was an interval of seven days between the injury and operation, and a further period of six days between the operation and the commencement of lengthening. We have asked ourselves the question, whether or not the trauma incident to the operation increased the production of callus at a stage when preosseous tissue was being formed, and furthermore, did the stimulation provided by traction incite a more rapid

and extensive proliferation in an already active osteogenic tissue? The roentgenologic evidence was sufficiently suggestive to warrant, in a case of lengthening presented later in this communication, utilization of this possible critical period in bone formation.

In the following cases a new apparatus was employed, the principles of which were suggested by one of our associates, Dr. Francis E. West.

Description of Apparatus.—This consists of the following parts (Fig. 6 a and b):

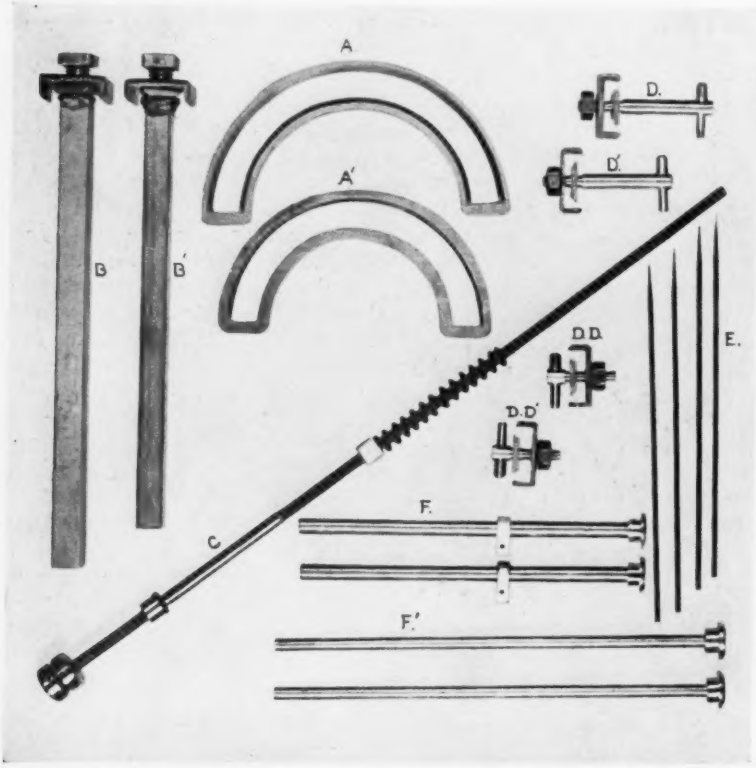

FIG. 6(a).—Oblique pin apparatus. (A) Half-hoops with curvilinear notches, (B) Hollow telescoping segments, (C) Threaded traction bar with nut and recoil spring, (D) Clamps with adjustable cylinders for pins, (E) Stainless steel drill pins, (F) Telescoping cylinders for support of control pins.

(A) Two half-hoops with curvilinear slots.

(B) Two hollow telescoping segments, each seven inches in length, equal in cross-section, inner segment being one-half inch wide and the outer nine-sixteenths of an inch wide.

(C) Four clamps with adjustable rotating cylinders to hold the traction pins.

(D) A threaded traction bar, 15 inches in length, one-quarter of an inch in diameter, with a recoil spring, three inches long.

(E) Four stainless steel drill pins, six inches long and one-eighth of an inch in diameter.

(F) Two telescoping cylinders for control pins.

In assembling the apparatus, the hollow segments are telescoped over each other. The threaded traction bar with the recoiled spring is passed down their centers and the ends are fixed to the two half-hoops by nuts and screws. The four adjustable clamps are now attached to the two half-hoops, two are placed so that their metal cylinders lie above and below the metal hoops; the other two with their cylinders lie on the medial surfaces of the hoops.

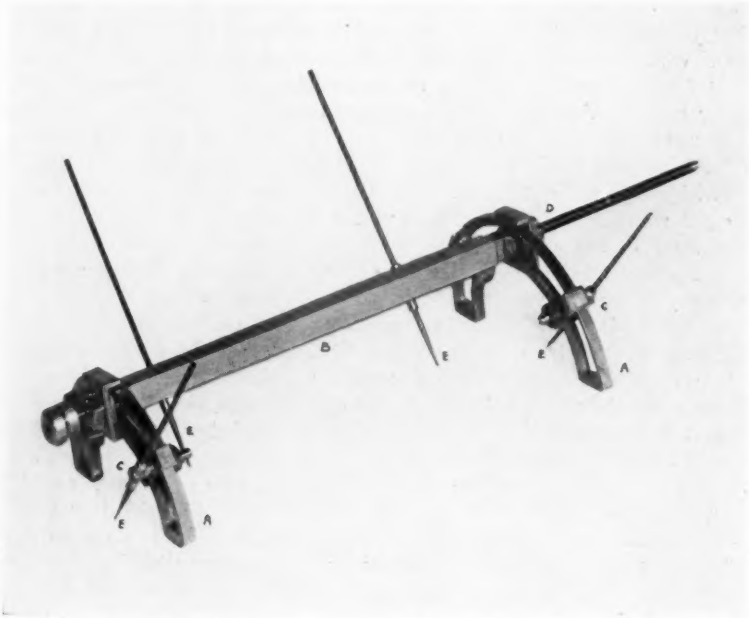

FIG. 6(b).—Oblique pin apparatus, assembled: (A) Half-hoops with curvilinear notches, (B) Rectangular telescoping segments, (C) Adjustable pin clamps, (D) Threaded bar with nut and recoil spring, (E) Four stainless steel pins.

During the application, the apparatus is held over the anterior surface of the leg by an assistant. The four clamps with rotating cylinders are moved along the curvilinear notches in the half-hoops until the cylinders point in an oblique direction towards the middle of the lateral and medial surfaces of the upper and lower ends of the tibia. The pins are then passed through the cylinders and turned through the corresponding cortices of the shaft of this bone. All four pins also pass through the posterior cortex of the tibia. With the pins engaged, the clamps holding the cylinders are fixed to the curvilinear notches in the half-hoops.

To secure further control of the fragments we have included in our illustration telescoping cylinders which may be attached to the outer segments of the upper and lower hoops on both sides of the leg. To these cylinders, adjustable pins may be attached with their central ends set against the lateral

surfaces of the terminal portions of the upper and lower fragments of the tibia. In Cases 4 and 5, with osteotomy of the tibia in the transverse plane, we employed a single control pin set against the anterior surface of the lower end of the upper fragment. We have not used control pins with the osteotomy of the tibia performed in the anteroposterior plane.

Case 4.—L. B., male, age 16. Admitted, March 3, 1937.

Chief Complaint.—Shortening of the right leg and deformity of the foot.

History.—Acute anterior poliomyelitis in 1931, with residual paralysis affecting the right leg. His former treatment consisted of braces and physical therapy.

Physical Examination.—There was atrophy of the right lower extremity with a moderate amount of power in the soleus, gastrocnemius and the extensor hallucis longus. The foot was held in a position of valgus. There were two and one-quarter inches of shortening with two inches confined to the tibia and fibula.

First Stage Operation.—March 10, 1937: Through an anterolateral incision, the common peroneal nerve, popliteal and anterior tibial vessels were exposed. The fibula was sectioned obliquely. The posterior cortex of the tibia was sectioned transversely just below the lower end of the linea poplitea. At the outer extremity of this osteotomy a linear division was made at the cortex at the middle of the lateral surface of the tibia extending downward a distance of about three and one-half inches. A plaster encasement was applied for support.

Second Stage Operation.—March 22, 1937: On reopening the lower portion of the operative wound, we discovered that there had been almost complete union of the soft part structures and fibula. These tissues had to be separated a second time. The oblique pins were inserted into the upper and lower ends of the tibia and the traction apparatus was applied. With a power-saw, the osteotomy was completed by dividing the cortex of the medial surface of the tibia paralleling the cut made through the outer cortex of this bone at the first operation. These linear cuts were joined below by a transverse division of the crest of the tibia. A fifth pin was attached to the rectangular piece of the traction bar and fitted against the anterior aspect of the cortex of the upper fragment. The tendo achillis was not lengthened.

Postoperative Notes.—Lengthening in this patient was gradually secured with the knee held in the flexed position. A gain of one and three-quarter inches was recorded, with good alignment. There was slight anterior tilting of the lower end of the upper fragment which was controlled by the fifth pin. After the desired length was secured, extension of the knee was completed in 10 days. The apparatus was removed 58 days after lengthening was begun, and a plaster encasement was applied for immobilization.

May 30, 1937.—A walking plaster encasement was applied. The patient had full length, with union in excellent alignment, and there was a marked improvement in function. The deformity of the foot was corrected, subsequent to the lengthening, by stabilization.

Case 5.—T. F., male, age 15. Admitted, March 7, 1937.

Chief Complaint.—Shortening of the right leg.

History.—Anterior poliomyelitis at the age of three, with involvement of all four extremities. There had been complete return in function except in the right lower extremity.

Physical Examination.—There was a marked shortening, complete paralysis of this extremity and valgus deformity of the foot. The shortening amounted to two and one-quarter inches, which was confined to the leg.

Operation.—March 9, 1937: The operation was performed in two stages in exactly the same manner as in Case 4. Again, there was a tendency for the lower end of the upper fragment to tilt forward and a fifth pin was used for control. Alignment was then easily maintained. A gain of two inches was secured. There were no important com-

plications other than a slight sloughing at the entrance of the control pin, which cleared up rapidly after the pin was removed. The apparatus was taken off in two months.

Postoperative Notes.—June 15, 1937: The patient was wearing a walking plaster splint for protection. Roentgenograms showed union, with good alignment, and a gain of two inches in length.

September 1, 1938.—There was union with good alignment. Function was markedly improved.

In Cases 4 and 5, there was a moderate anterior tilting of the lower end of the upper fragment of the tibia. This was controlled in part by flexion of the knee, but complete contact of the fragments could only be maintained by the use of a fifth pin. We must take into account, however, that the tendo achillis was not lengthened in either of these cases and was undoubtedly the cause of the forward tilting of the lower end of the upper fragment.

Further dissections have shown that the malalignment of the tibial fragments in the anteroposterior plane is caused by the tension thrown upon the intact gastrocnemius muscle. The soleus muscle plays no part in the production of this deformity because its origin has been released. Lengthening of the tendo achillis is not sufficient to relax the gastrocnemius. We have found the logical method to be the division of the tendon of the gastrocnemius where it joins the tendon of the soleus. The gastrocnemius muscle is then rendered slack by the transplantation upward of its tendinous portion to the fascial surface on the posterior aspect of the soleus. We have fixed this tendinous portion of the gastrocnemius in its new position by silk sutures and have reinforced the junction by using the tendon of the plantaris as a living suture.

Another lesson learned from our experience with Cases 4 and 5, is that the interval separating the two stages of operation should not be longer than five or six days. If this period is exceeded, the tissues become firmly reattached and require a second separation.

In the next patient we tried to reproduce the same conditions for the formation of bone as were present in Case 3. These did not exactly coincide, however, because we did not strip the periosteum during the second stage of the procedure. In analyzing the problem we planned a supplemental bone-grafting operation in case there was not sufficient formation of callus.

Case 6.—M. D., female, age 18. Admitted, October 17, 1937.

Chief Complaint.—Shortening of the left lower extremity.

History.—Acute anterior poliomyelitis at age two, with residual paralysis in the trunk, upper and lower extremities. She had conservative treatment until 10 years of age, when the left foot was stabilized. In 1933, the tendo achillis was lengthened on the left side. In 1935, she had corrective jackets and a fusion operation upon her spine. At present, she complains of lack of balance due to shortening of the left lower extremity. The balance and gait were improved by a lift on the left shoe.

Physical Examination.—There was extensive involvement of the muscles of all four extremities and the trunk. She walked with a bilateral gluteus medius gait. She had difficulty in maintaining balance without a lift of one and one-half inches on the left shoe. The gait was improved by walking on boards of the same height. There was two inches of shortening, one and one-quarter inches being present in the leg.

First Stage Operation.—October 20, 1937: Under general anesthesia, an oblique inci-

FIG. 7(a).—First stage. Insert shows incision. Illustration shows origin of muscles and relation of common peroneal nerve to biceps.

sion was made through the skin and periosteum on the anterior surface of the left tibia at the junction of the upper and middle thirds. The periosteum was stripped from the crest and the adjacent bone. An oblique osteotomy, two inches in length, was performed with drill and osteotome. A plaster encasement was applied.

Second Stage Operation.—October 26, 1937: A vertical incision was made on the posterior surface of the leg extending from the lower margin of the popliteal space to the junction of its lower and middle thirds. After retraction of the lesser saphenous vein, the common peroneal and cutaneous nerves, the two heads of the gastrocnemius were separated from each other down to their union with the tendinous portion of the soleus. With the neurovascular bundle freed and retracted posteriorly, the origins of the soleus and the tibialis posterior were reflected subperiosteally from the posterior aspect of the tibia and fibula and the fibrous arch between these two bones. An oblique osteotomy was performed through the neck and upper portion of the fibula. The popliteus muscle was turned upward and an osteoperiosteal graft, two inches in length, was cut from the posterior surface of the upper fragment just above the osteotomy. With lengthening, this graft would bridge the osteotomy. The tendinous insertion of the gastrocnemius was transplanted upward a distance of two inches to the posterior aspect of the soleus.

November 4, 1937.—Under general anesthesia, the oblique pin apparatus was applied. The upper pins were placed in the tibia while the lower pin was passed through the fibula and tibia. A Mathews wire was then inserted in the os calcis. The leg was supported on an adjustable splint with the knee held in 45° of flexion. With the lengthening, traction was also applied to the pin through the os calcis.

November 9, 1937.—There was a tilting forward of the lower end of the upper fragment which was controlled by placing a pin against its anterior cortex.

Postoperative Notes.—December 16, 1937: Thirty-six days after the beginning of lengthening, two inches had been gained. The alignment was satisfactory together with the formation of some callus. The knee was being gradually extended with the lengthening apparatus in position.

September 1, 1938.—The gain in length of two inches has been maintained with good alignment. Sufficient callus did not form to insure union. A bone graft was performed at the site of the lengthening operation in order to reinforce the callus. The patient remains in the hospital and an end-result cannot be given at this time.

Appended is a description, in detail, of the anatomic dissections which were employed. In some instances these dissections were carried out completely, and in others, only partially. We have also discussed a method of performing an osteotomy of the tibia in the vertical plane. In our opinion, this type of osteotomy provides for the maximum retention of the origin of muscles to the descending fragments with minimum separation of the periosteum. It also preserves the nutrient vessels of the tibia and fibula.

Description of the Dissections in the Above Operation.—First Stage: The incision commences over the tendon of the biceps femoris on the posterolateral aspect of the knee and is carried downward along the course of this tendon to the neck of the fibula. From thence it curves obliquely across the anterolateral aspect of the leg to a point about one inch below the level of the tibial tubercle; there, it follows the crest of the tibia to the junction of the middle and lower thirds of the leg (Fig. 7 a). In general, the incision follows the course of the common peroneal nerve in its upper part and the anterior tibial vessels and nerve in their lower parts. The common peroneal nerve is immediately exposed under cover of the medial border of the biceps tendon. It is then traced to the lateral aspect of the neck of the fibula where it is firmly

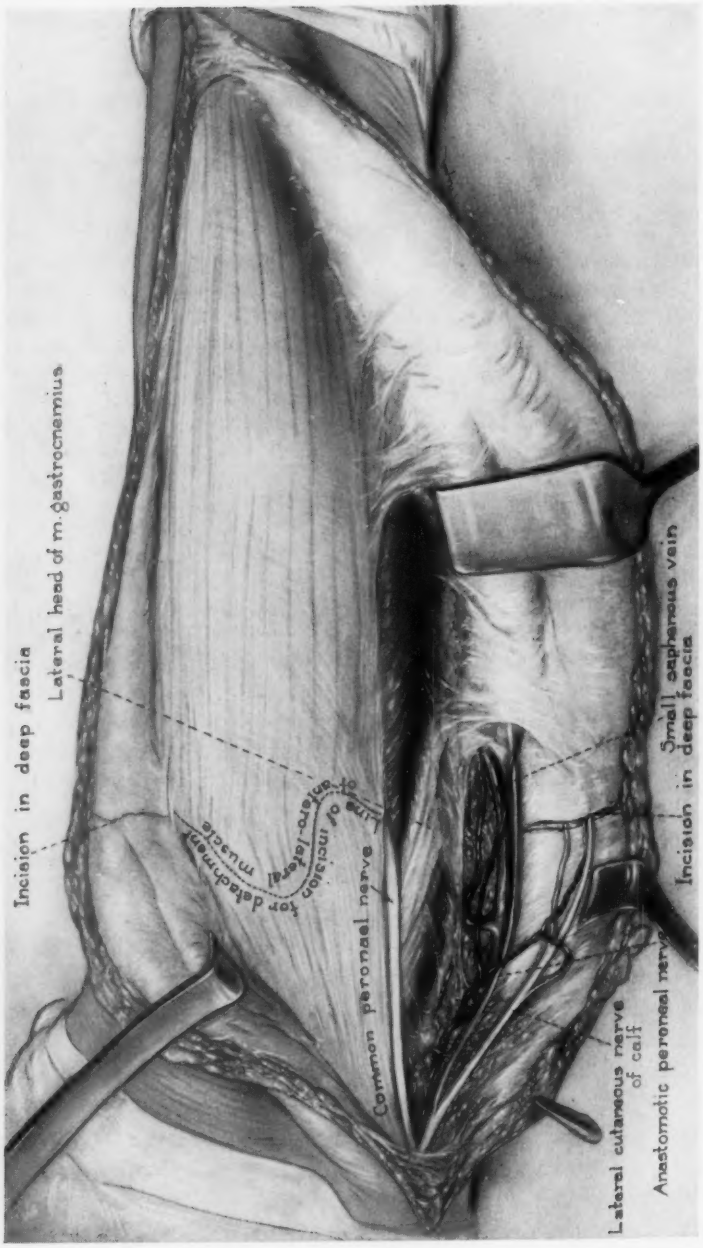
Incision in deep fascia
Lateral head of m. gastrocnemius
Line of incision for detachment of antero-lateral muscle
Common peroneal nerve
Lateral cutaneous nerve of calf
Anastomotic peroneal nerve
Small saphenous vein
Incision in deep fascia

FIG. 7(b).—First stage. Illustration shows the cutaneous structures. Note method of dividing deep fascia and line of detachment of origin of muscles.

bound down by fascial extensions from the biceps tendon to the deep fascia of the leg. Incision of this fascia constitutes an important step because it frees the nerve from its main point of fixation. Flexion of the knee will now demonstrate a very considerable laxity of the nerve, amounting to as much as one and one-half inches. The nerve can then be readily followed to its division into three chief branches, the upper being the recurrent articular, the intermediate, the deep peroneal and the lower, the superficial peroneal. These branches with their subdivisions are now traced to their entrance into the muscles. In dissecting this nerve, it is well to look for the lateral cutaneous and the anastomotic peroneal branches where they are given off the main trunk

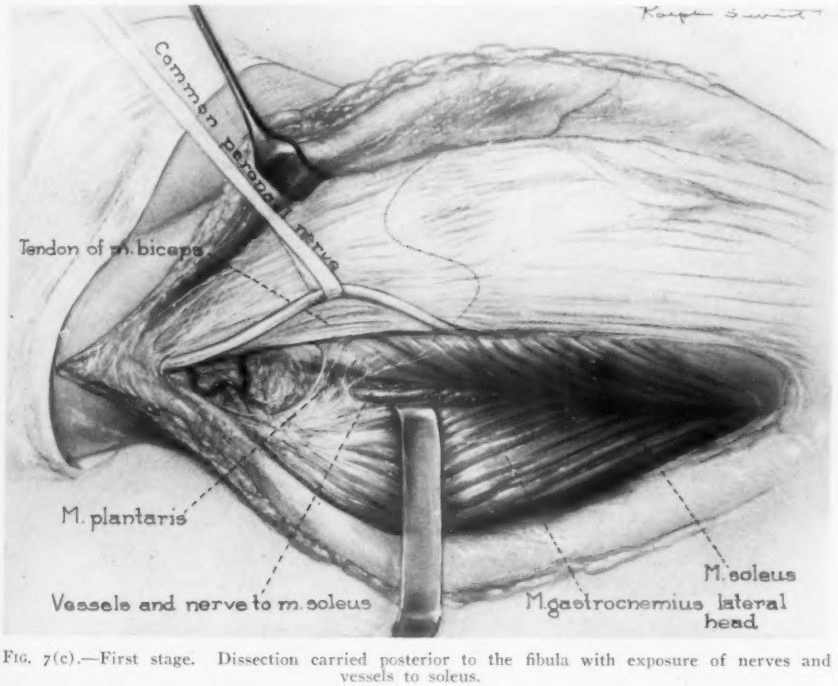

FIG. 7(c).—First stage. Dissection carried posterior to the fibula with exposure of nerves and vessels to soleus.

about two finger breadths above the external condyle, either separately or from a parent trunk. The deep fascia is incised transversely as far laterally as the lesser saphenous vein, taking care to avoid injury to the cutaneous nerves, *i.e.*, the lateral cutaneous nerve of the calf and the anastomotic peroneal nerve (Fig. 7 b).

Behind the head and neck of the fibula, the dissection is carried to the lateral head of the gastrocnemius (Fig. 7 c). This muscle is retracted posteriorly, exposing the origin of the soleus from the posterior aspect of the head and neck of the fibula. Its nerve and vessel supply may be seen entering its superficial surface near its upper border. The plantaris muscle is identified deep to the medial margin of the lateral head of the gastrocnemius. The plantaris is an important landmark since the junction of its belly and tendon

lies directly over the major vessels and nerves. These structures should be carefully freed from the surrounding tissues. The popliteal artery is found lying upon the popliteal muscle and at its inferior border, and divides into the anterior and posterior tibial arteries. The finger is inserted beneath the fibrous arch of the soleus and this muscle may be lifted backward while its origin is reflected subperiosteally from the fibula. In freeing this muscle great care is exercised to avoid injury to its nerve supply and the anterior tibial vessels. This is the most critical and delicate stage of the dissection, as when the attachment of the soleus is released from the fibula, the anterior tibial vessels are exposed coursing forward through the interosseous membrane. At this point the dissection is carried on to the anterior aspect of the upper end of the

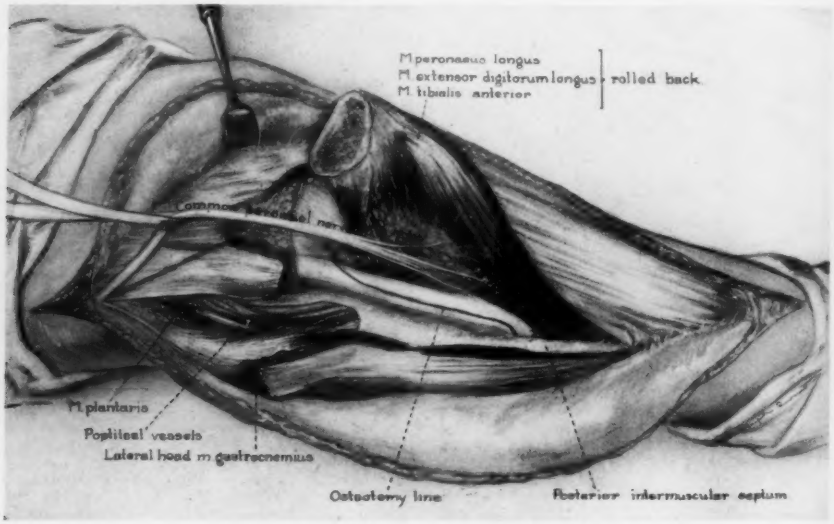

FIG. 7(d).—First stage. Showing osteotomy of fibula.

fibula. The anterior and posterior intermuscular septa are isolated and freely incised. A curved incision is also carried down to the bone across the head of the fibula and along the margin of the attachment of the peroneus longus, extensor digitorum longus and the tibialis anterior muscles to the lateral condyle of the tibia (Fig. 7 d). These attachments are deflected with a shaving of bone from the head of the fibula and the lateral condyle of the tibia. As the muscles are turned forward and the common peroneal nerve lifted out of the way, the interosseous membrane is reached from its anterior aspect. The anterior tibial vessels are met with again in the extensor compartment. The interosseous membrane and the tibialis posterior are separated from the upper end of the fibula. The popliteal vessel can now be retracted freely backward because its divisions have been freed at their points of fixation to the interosseous membrane and the fibrous arch of the soleus.

The next step is the division of the bone: A special retractor is passed around the medial surface of the neck of the fibula to protect the blood vessels

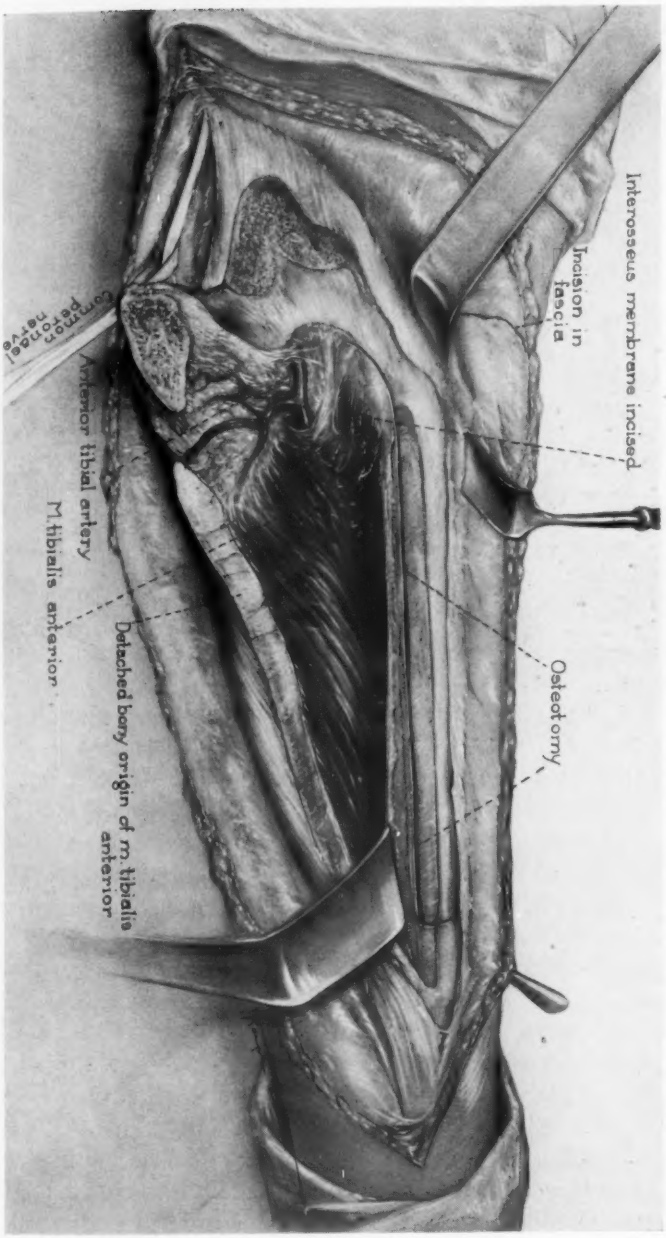

FIG. 7(e).—First stage. Popliteal and anterior tibial arteries exposed. Linear osteotomy of the lateral cortex of the tibia extending from arch above to the transverse osteotomy of its crest below. Method of detaching origin of muscles with bone flaps.

and nerves. The common peroneal nerve is retracted upward and forward. The fibula is sectioned obliquely by a saw cut or by drill and osteotome. The osteotomy, about two and one-half inches in length, begins one-half inch below the tibiofibular joint and extends downward and laterally. With a saw, or if the operator prefers, a drill, a long oblique section is made through the outer cortex of the tibia. This section begins about one-half inch below the apex of the arch and passes downward and gradually forward upon the antero-lateral surface of the tibia until it lies just below the tubercle of the tibia and posterior to the crest. At this point, a vertical section of the bone is continued down to the level of the junction of the middle and lower thirds of the bone. At the lower end of this section, a transverse osteotomy is made through the crest and cortex of the subcutaneous surface of the tibia (Fig. 7 e).

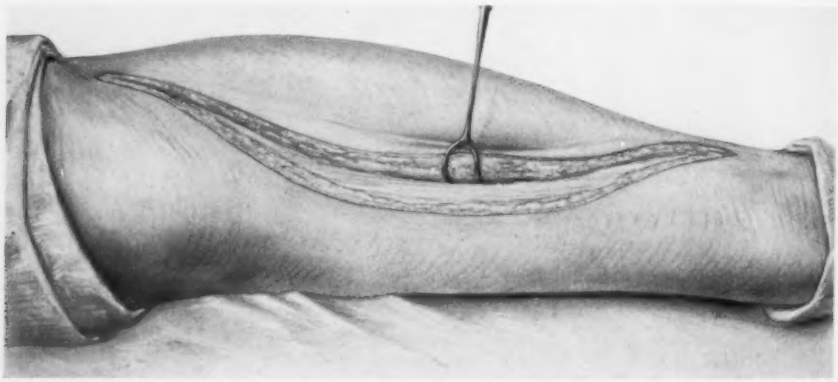

FIG. 8(a).—Dissection illustrating anatomic approach through posteromedial incision (second stage): Curvilinear incision, posteromedial aspect of leg.

The first stage is completed with suture of the detached origin of the muscles to the surrounding tissues to obliterate the dead space. The anterior margin of the peroneus longus and the lateral margin of the soleus are sutured to prevent contact of the common peroneal nerve with the fibula.

Second Stage.—The lengthening apparatus with the oblique pins is applied. With the knee flexed to 30° and externally rotated, a curvilinear incision is made over the posteromedial aspect of the calf. It begins over the origin of the inner head of the gastrocnemius and ends at the junction of the middle and lower thirds of the leg where the tendons of the gastrocnemius and soleus merge to form the tendo achillis. The summit of the convexity is placed one-half inch behind the medial border of the tibia. This avoids injury to the greater saphenous vein and the saphenous nerve (Fig. 8 a).

A few veins are ligated as they cross the wound in the subcutaneous tissue. The deep fascia is incised along the line of the skin incision. At the upper end of this fascial incision, a transverse division is made in the lateral direction through the deep fascia to the margin of the small saphenous vein. This transverse division of the fascia meets with the transverse division of the fascia made in the first stage. At the lower margin of the wound a similar transverse

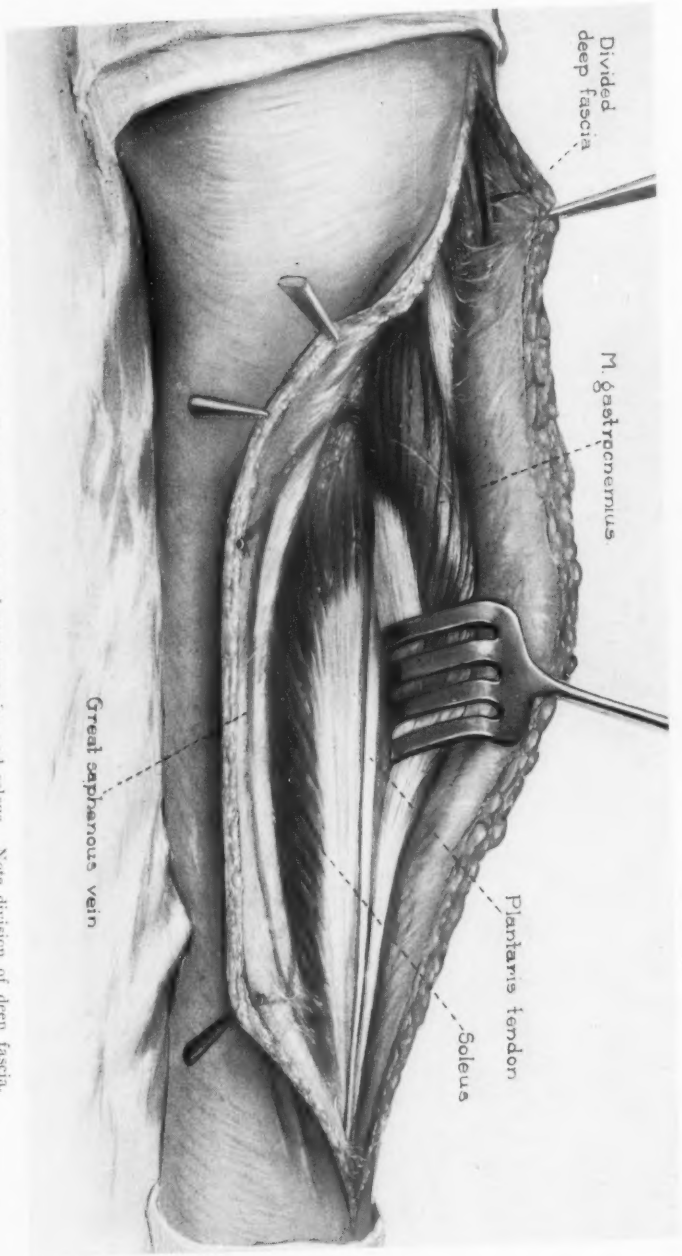

FIG. 8(b).—Second stage. Exposure of tendon of gastrocnemius and soleus. Note division of deep fascia.

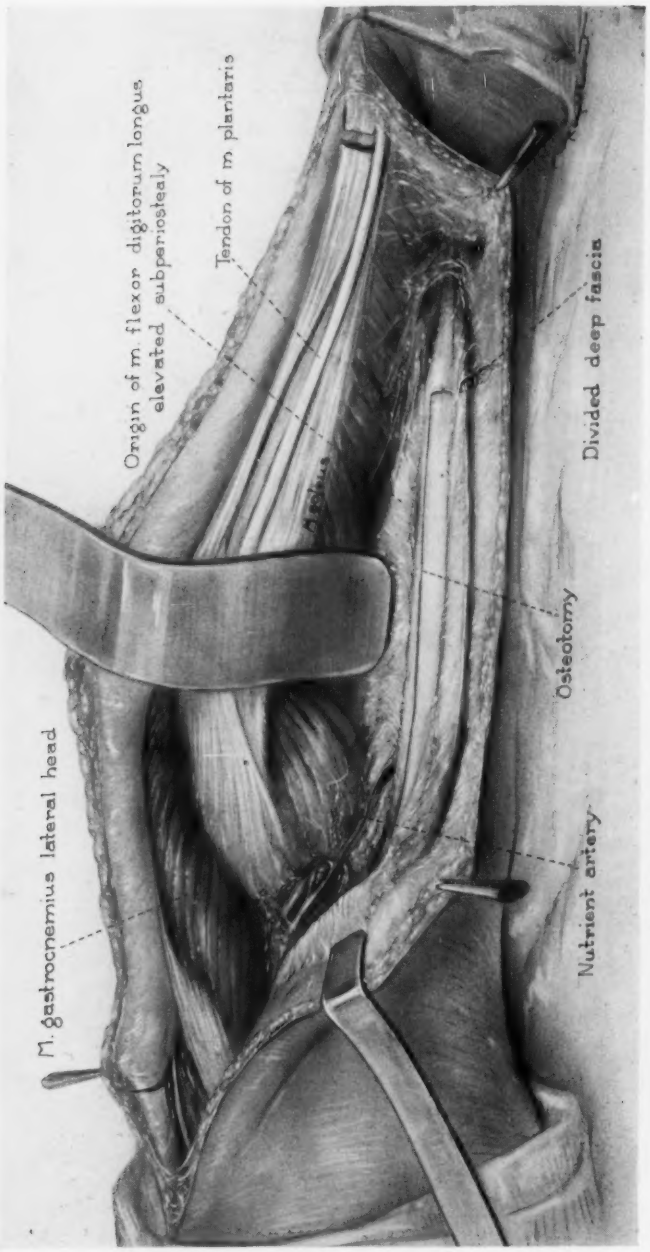

FIG. 8(c).—Second stage. Osteotomy of tibia showing nutrient vessel.

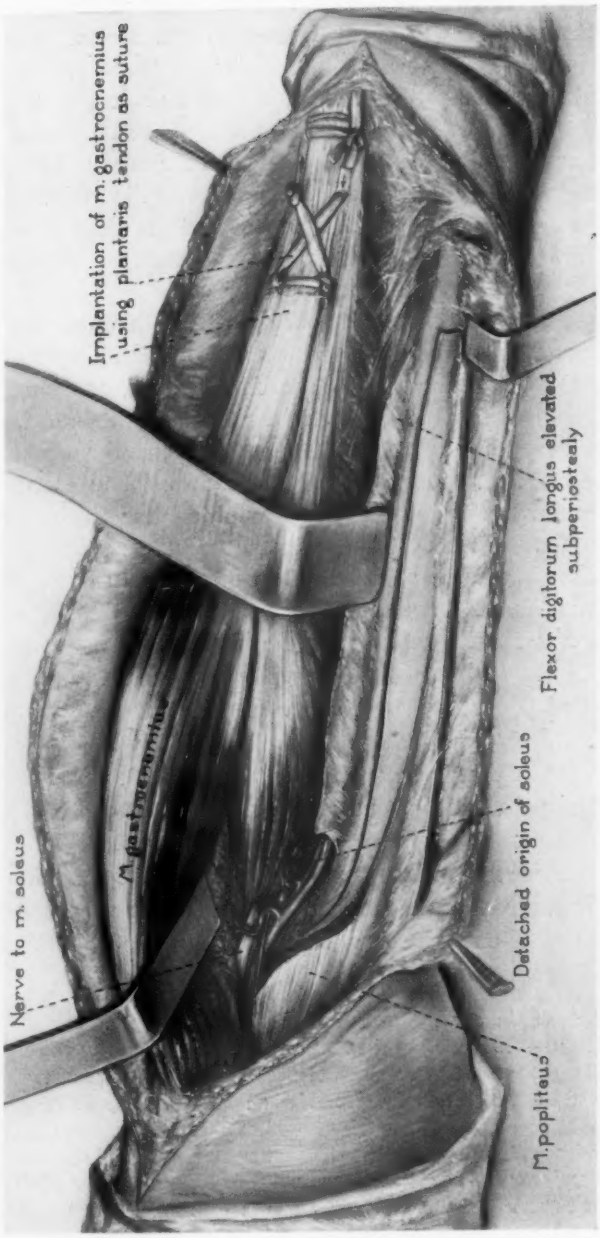
Implantation of m. gastrocnemius using plantaris tendon as suture
Nerve to m. soleus
M. gastrocnemius
Detached origin of soleus
Flexor digitorum longus elevated subperiostealy
M. popliteus

FIG. 8(d).—Second stage. Linear osteotomy of the posterior cortex of the tibia; extending from arch above to transverse osteotomy below. This division of posterior cortex parallels the osteotomy of the lateral cortex of first stage, thus completing the separation of the fragments. Method of implantation of the gastrocnemius.

incision of the fascia is made in an anterior direction until it meets the transverse division of the periosteum on the subcutaneous surface of the tibia at the level of the transverse osteotomy. The fascial incisions of the first and second stages of operation, together with the division of the periosteum, complete an oblique circumferential section of the fascia and periosteum. The tendon of the gastrocnemius is freed from the tendon of the soleus and sectioned obliquely (Fig. 8 b). This tendon is then implanted into the soleus at a higher level. The distance upward of this transplantation is equal to the amount of length desired. Here, it is secured by silk sutures which are reinforced by the tendon of the plantaris, this being utilized as a living suture (Fig. 8 d). With retraction of the gastrocnemius, the popliteal vessels and the tibial nerves are freed to expose the origin of the muscles in the region of the fibrous bony arch formed by the upper ends of the tibia and fibula.

The soleus muscle is detached at its origin from the posterior aspect and internal border of the tibia, removing with it the superficial layer of the cortex (Fig. 8 c and d). As this muscle is turned downward, care should be taken not to injure the popliteal vessels, the tibial nerve and the branches of supply to the soleus and the tibialis posterior. The nutrient vessels of the tibia, associated with the muscular branches of the soleus, are found entering the bone obliquely an inch or two below the oblique popliteal line on the lateral side of the posterior surface of the shaft. The insertion of the popliteus is reflected upward from the oblique line sufficiently to expose the posterior border of the tibia as it ascends to the apex of the arch. At this place, the origin of the tibialis posterior and the attachment of the interosseous membrane are freed for a distance of one and one-half inches. In this denuded area a special retractor is inserted protecting the main vessels and nerves, while the bone is sectioned with a drill or saw, beginning one-half inch below the tibiofibular arch. The osteotomy through the posterior cortex parallels at first the oblique line and then passes down just lateral to the medial border of its shaft to the junction of the middle and lower thirds where it meets the posterior extremity of the transverse osteotomy of the first stage of the operation (Fig. 8 d). Care is taken to insure that the fragments are free. The extension apparatus is now tightened until one can see a distinct separation of the fragments. The wounds are closed and the leg is supported in flexion.

Case 7.—P. E., male, age 16. Admitted, December 27, 1937.

Chief Complaint.—Shortening of the left leg.

History.—The patient had tuberculosis of the left hip at the age of two. There were draining sinuses at the site of the infection. He had an arthrodesis of the left hip December 31, 1925. He had a second arthrodesis of the left hip April 13, 1929, and an osteotomy of the left femur November 3, 1932. The sinuses had stopped draining since August, 1932.

Physical Examination.—The left hip was arthrodesed in a position of slight abduction. There was about 20° flexion. The knee was markedly unstable. It presented about 10° valgus deformity which could be increased to 30°. Flexion of the knee was possible to 90°. The knee could be completely extended. There were four and one-half inches of shortening in the tibia and fibula and one-half inch of shortening in the femur.

Operations.—December 31, 1937, and January 17, 1938: These were performed in two

stages. The osteotomy of the tibia and fibula was performed in the anteroposterior plane as described above. The oblique pin apparatus was applied.

Postoperative Notes.—The lengthening process was begun 10 days after the completion of the second stage. It was continued until February 21, 1938, when there was a gain of two and one-half inches.

March 10, 1938.—The apparatus was removed and a Mathews wire was passed through the os calcis. The ends of this wire were incorporated in a plaster encasement which extended from the toes to the groin. He was discharged April 29, 1938.

COMMENT.—The patient was examined at intervals, and at the time of his last examination, October 9, 1938, he was bearing weight with the aid of a plaster encasement for protection. There was good alignment with bony union and a gain of two and one-half inches in length. There was no deformity of the foot or ankle and the tarsal joints had free motion in all directions. He had excellent power in the muscles whose origins were freed (Fig. 9).

FIG. 9.—Case 7 showing length secured, with good alignment and formation of callus. Note the bridge of new bone forming where the muscles were detached from the arch formed by the upper ends of the tibia and fibula.

This case demonstrates that the freeing of the origins of the muscles to permit adequate lengthening does not interfere with the retaining of their functions. The absence of deformity of the foot, ankle and at the site of osteotomy was a striking feature in this case.

Postoperative Lengthening.—The lengthening process is carried out in much the same manner as described in earlier publications. Our experience has shown that one-sixteenth of an inch of length per day can be gained with little discomfort to the patient. In a few instances, we have increased the rate of lengthening to one-eighth of an inch per day and, in one case, gained one and one-half inches in 20 days. We do not recommend this manner of rapid lengthening, however, because it generally causes considerable pain. Daily measurements are recorded and roentgenograms are taken at intervals to check the position of the fragments and the amount of callus which has formed. Usually, sufficient callus has developed in 10 to 12 weeks to permit gradual extension of the knee. In some cases we have used a supporting splint which was devised by our instrument and brace-maker, Mr. August Kern, which adequately supports and allows minute adjustments during the lengthening and during the gradual extension of the knee. When the knee has been completely extended, the apparatus is removed and the leg is immobilized in a plaster encasement which extends from the toes to the groin. Weight-bearing with support is generally allowed in four or five months. To lessen the chances of fracture, we have insisted on the use of a protective weight-bearing appliance until the callus is

completely formed with restoration of the medullary canal, a period usually of nine to 12 months.

SUMMARY AND CONCLUSIONS

The writers have described a technic of operation for lengthening of the tibia and fibula which is based on new principles.

(1) These principles involve complete division of the deep fascia of the leg, the intermuscular septa and the interosseous membrane, as well as the freeing of all of the important blood vessels and nerves at the upper portion of the leg.

(2) Special osteotomies have been devised, which provide for retention of the maximum portion of the origin of the muscles which pass from the leg to the foot and permit them to travel downward with the descending fragments.

(3) Incisions provide for freeing the blood vessels and nerves from their points of fixation, thus permitting relaxation of these structures during the lengthening. The operation also provides for the preservation of the nutrient vessels of the tibia and fibula, and with the minimum reflection of the periosteum there is but little disturbance of the blood supply to these bones.

(4) A new apparatus has been developed which we believe will give better control of the fragments, and offer less chance of infection of the pin wounds.

(5) Our recent operations comprise seven cases, all of which have been handled in a somewhat different manner.

(6) As a result of our practical experience, we feel that the operation is based on sound principles, all designed to avoid complications which are certain to occur in some instances with the previous methods described.

(7) In the seven cases studied with the newer methods which we have devised, the anterior tilting of the upper fragment has been decidedly less marked and we believe it will be entirely controlled by flexion of the knee together with the recent method of transplantation of the gastrocnemius tendon. The internal bowing of the fragments of the tibia and the deformities of the knee and foot have been almost entirely eliminated. No important changes have been noted which could be attributed to injury to the blood vessels or nerves.

(8) We emphasize that the operation of leg lengthening is and in all probability always will be, a major undertaking with the possibility of serious complications. The procedure demands an intimate knowledge of anatomy, a careful study of every stage of the operation and postoperative care. We believe that this is not an operation for the uninitiated and should be reserved for those whose experience renders them competent to perform this technically difficult and delicate procedure. In its present stage of development, no final conclusions are offered. We would advise, however, that no one should attempt it without carefully reviewing every detail of our work and then supplementing it with a thorough anatomic study.

(9) In the beginning of our work on bone lengthening, we designed procedures which were conservative in character. Recently, we have carried

out more radical operations to avoid complications which arose with these methods. We are convinced that with further study and experience, a middle course will be found which will swing the pendulum again toward conservatism but at the same time will permit the attainment of the objectives desired.

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A CLINICAL CONSIDERATION OF THE METHODS OF EQUALIZING LEG LENGTH *

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IN ALL ages and by all races, inequality of leg length has been regarded as a disgraceful and crippling affliction. The disability resulting from it varies and is directly proportional to the amount of difference in the length of the two limbs. An individual who is otherwise normal can generally compensate for a discrepancy of as much as one inch by tilting the pelvis and walking with one hip higher than the other. When the difference is greater than this, a lift should be inserted under the shoe or an excessive curvature of the spine will be produced and symptoms of strain and fatigue may result. For a discrepancy of two to three inches a cork insert under the shoe is fairly satisfactory. When the shortening exceeds four inches a metal patten must generally be used and in extreme instances a wooden prosthesis constructed after the manner of an artificial limb.

Inequality of leg length often produces a bad psychologic effect, as the raised shoe is conspicuous whether walking or sitting. Every boy or girl demands that something be done to rid him of what is considered to be a badge of ignominy. The cost is also an important factor when one considers the expense of specially built shoes during a lifetime. The elevation of the shoe is apt to increase the instability of the already crippled extremity. Its weight is also objectionable in the case of individuals with partially paralyzed muscles or disabilities of the joints.

TABLE I

COMMON CAUSES OF INEQUALITY OF LEG LENGTH

Conditions	Lengthening	Shortening
Poliomyelitis		−
Chronic bone infections	+	−
Tuberculosis of hip		−
Tuberculosis of knee	+	−
Epiphyseal injuries		−
Congenital dislocations		−
Tumors	+	−
Hemiatrophy		−
Hemihypertrophy	+	
Congenital anomalies	+	−
Malunited fractures		−

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Discrepancy in leg length may be due either to retardation of growth in the short extremity or to overgrowth of the long one. Sometimes the same pathologic condition may cause shortening in one individual and lengthening in another. The more common causes are listed in Table I.

Different ways of dealing with instances of unequal leg length by surgical methods have been devised. They approach the problem from different angles and may be classified as follows:

I. Changing the Rate of Growth:
  (1) Stimulation of growth in the shorter extremity.
    (a) Local stimulation of bone growth.
    (b) Lumbar sympathectomy.
  (2) Retardation of growth in the longer extremity.
    (a) Epiphyseal arrest.

II. Surgical Reconstruction:
  (1) Bone lengthening of the shorter extremity.
  (2) Bone shortening of the longer extremity.

Although considerable pressure is often brought to bear upon the surgeon to correct inequality of leg length, he should never permit sentimental reasons to overcome his surgical judgment. An elevated shoe often affords the best solution of the problem. Careful observation of a patient's gait with a raised shoe should always precede any decision as to operative treatment. In crippling conditions, shortening is often only one of several factors responsible for the disability or limp. Ankylosis or deformity of the hip, knee or foot, or muscle weakness may be more disabling factors than the shortening and should receive appropriate treatment. Equalization of leg length when such other factors are ignored is likely to prove disappointing.

I. Changing the Rate of Growth.— (1) *Stimulation of Growth in the Shorter Extremity:* The hereditary, physiologic, metabolic and pathologic factors determining bone growth are too varied and complicated to discuss in detail. The longitudinal growth of the long bones is unique, in that it occurs only near the ends at the epiphyseal cartilage disks. Other body structures, even the periosteum, enlarge by general interstitial growth. If the causative agents of achondroplasia and gigantism could be isolated and used locally, accurate control of epiphyseal growth might be possible. Generalized increase or decrease in the growth of bones depends upon various systemic factors, many of them unknown.

It has often been observed that decreased function and/or decreased circulation cause subnormal epiphyseal bone growth as well as atrophy of the entire part. Conversely, increased local circulation is often accompanied by increased growth. Numerous pathologic conditions are sometimes associated with increased length of the affected extremity (Table II). Temporary or permanent hyperemia is found in all of them. As it is not feasible to reproduce any of these pathologic conditions for the purpose of stimulating the growth in a short extremity, many attempts have been made to induce hyperemia by other means.

TABLE II

PATHOLOGIC CONDITIONS ASSOCIATED WITH LENGTHENING OF AN EXTREMITY

(A) Congenital Conditions
  (1) Hemihypertrophy
  (2) Arteriovenous aneurysm
  (3) Recurring hemarthrosis in hemophilia
(B) Infections
  (1) Tuberculosis of knee (low grade)
  (2) Chronic osteomyelitis of femur or tibia
  (3) Chronic soft tissue infection
  (4) Syphilis
  (5) Femoral or iliac thrombosis
  (6) Elephantiasis
(C) Tumors
  (1) Giant cell tumor
  (2) Osteitis fibrosa cystica (diffuse unilateral type)
  (3) Neurofibromatosis (von Recklinghausen)
  (4) Hemangioma or lymphangioma
  (5) Large nevi
(D) Trauma
  (1) Fracture of femur
  (2) Removal of bone graft from tibia
  (3) Extensive periosteal stripping

Ollier,[46] in 1867, noted that irritation of the shaft of a bone produced acceleration in the rate of growth, and Kishikawa[40] found that ligation of the femoral vein, or injection of oil of turpentine into the marrow cavity, caused slight but definite increase in the growth rate. Meisenbach,[43] Bohlman[15] and others inserted numerous foreign materials into the region of the epiphyseal cartilage with the object of producing more rapid bone growth through local irritation. However, most of these substances caused retardation, and none of them accomplished the desired result. When the material inserted was definitely irritating or caustic there was often complete disappearance of the epiphyseal line. Brooks[18] found that small doses of roentgen ray (2 to 5 per cent S.E.D.) caused no stimulation. The most successful experiments were those of Wu and Miltner,[62] who produced an increase of 5 to 15 per cent in the growth rate of the extremities of young animals by extensive periosteal stripping.

Increased longitudinal growth following fracture of a growing bone has been noted clinically and experimentally. It cannot be considered compensatory as it commonly occurs even though there is no shortening due to the fracture. Ferguson[31] believed that the interruption of the metaphyseal blood supply with resulting hyperemia in the epiphyseal region was the cause of this increased growth rate. Based upon this assumption, stimulation of growth was attempted in a number of patients by drilling the cortex near the epiphysis and curetting across the marrow cavity. A gain of one-twelfth to one-eighth of an inch was reported three to five months after operation.

Wu and Miltner,[62] and Compere and Adams[27] were unable to produce, experimentally, any stimulation of bone growth by the method advocated by

Ferguson. Brockway,[19] Chandler,[23] and Compere and Adams observed definitely increased growth in normal tibiae from which a graft had been removed. The latter two, after an extensive experimental and clinical study, concluded that gross trauma involving a considerable portion of a long bone and requiring a lengthy period of repair was the inciting factor. In their opinion the increased growth rate was directly associated with the local hyperemia and continued only during the period of increased vascularity.

The problem of producing an increased blood supply over a prolonged period presents great difficulties. Lumbar sympathectomy apparently accomplishes this better than any local procedure yet devised. Although the experimental attempts to stimulate growth by lumbar sympathectomy in animals have been uniformly unsuccessful, in children it is known to produce a lasting hyperemia, and many of these patients show definite gain in the rate of growth on the operated side. Stewart[55] noted one-half of an inch lengthening in two out of six patients who had had unilateral sympathectomy for spastic hemiplegia. Harris and McDonald[36] reported increased growth of one-half to one inch in three patients upon whom unilateral sympathectomy had been performed for Hirschsprung's disease.

These authors examined 46 out of 100 patients with poliomyelitis, who had had unilateral lumbar sympathectomy to improve circulation and stimulate growth. They stated that there was always some increase in the growth rate. In 21 of these, the improved vascularity resulted in a decrease in the discrepancy between the two extremities. This decrease amounted to one inch in two instances, three-quarters of an inch in four, and in the other 15 it was one-half of an inch or less. In eight, the hyperemia was sufficient to prevent any further increase in discrepancy. In 17, the discrepancy between the two extremities increased, but less rapidly than before the operation. According to these authors there is a basic rate of growth which in normal legs is stimulated by normal muscle activity and a normal blood supply. Sympathectomy improves only the latter and is not very effective in a severely paralyzed extremity. There are probably other factors such as diminished weight bearing which influence the leg growth after paralysis. It is even possible that there is a direct control of growth by special cells in the central nervous system, and that these, as well as the anterior horn cells, are affected by the virus of poliomyelitis.

Although lumbar sympathectomy may produce a prolonged hyperemia and is well worth while for the relief of chilblain and pain associated with poor circulation, the increase in growth is too little and too inconstant to recommend it as a method of equalizing leg lengths.

At the Hospital for Ruptured and Crippled, a small number of paralytic cases have been treated with diathermy to the epiphyses about the knee of the shorter extremity. In several instances there has been no further increase in the discrepancy between the two legs. Even if these treatments could be given daily or twice daily for a period of years, one would hardly expect as much improvement as from lumbar sympathectomy. We must, therefore, conclude that attempts to stimulate epiphyseal growth have not

been successful enough up to this time to warrant their clinical application.

(2) *Retardation of Growth in the Longer Extremity.*—Diminution or complete cessation of longitudinal growth occurs even more commonly than increased growth. The same abnormal conditions which cause stimulation frequently cause retardation, especially if the pathologic process actually involves the epiphyseal line. Any lesion associated with diminished circulation or gross trauma to the region of the growing cartilage disk is apt to produce partial or complete arrest of growth (Table III). Uneven growth with angular deformity is even more serious than uniform shortening.

TABLE III

PATHOLOGIC CONDITIONS ASSOCIATED WITH SHORTENING OF AN EXTREMITY

(A) Congenital Conditions
  (1) Unreduced congenital dislocation of hip
  (2) Congenital absence or partial absence of a long bone
  (3) Congenital hemiatrophy
  (4) Chondrodysplasia
  (5) Other congenital anomalies
(B) Infections
  (1) Poliomyelitis
  (2) Tuberculosis of hip or knee
  (3) Suppurative arthritis of hip, knee, or ankle
  (4) Osteomyelitis of femur or tibia
(C) Tumors
  (1) Osteitis fibrosa cystica (diffuse type)
  (2) Osteochondroma
  (3) Giant cell tumors
  (4) Other tumors
(D) Trauma
  (1) Slipping of upper femoral epiphysis
  (2) Other epiphyseal separations
  (3) Fractures involving epiphyseal cartilage disks
  (4) Operative trauma to epiphysis
  (5) Roentgenotherapy for conditions near the epiphyseal line
  (6) Malunited fractures

Although short extremities and growth deformities of the bones have been observed for years, Phemister[49] was the first intentionally to limit longitudinal bone growth by surgical means. He described a simple procedure which consisted of removing small bone grafts from each side of the lower end of the femur or the upper end of the tibia. These were taken largely from the diaphysis but extended just across the epiphyseal line. The epiphyseal cartilage plate was exposed by this removal and a large area of it curetted. The grafts were turned end-for-end and reinserted across the epiphyseal line. No postoperative support was required. Compere[25] stated that this operation had been performed in more than 100 cases at the University of Chicago Clinics, without complications.

Brooks[18] and others have shown that proliferation of the cartilage cells of the epiphyseal line can be delayed or even completely inhibited by exposure to roentgen rays. No attempt has been made to apply this method clinically, as serious damage to the adjacent articular structures is almost inevitable.

Many of the attempts to stimulate bone growth, contrary to expectations, produced retardation or even complete cessation, and it is possible that some method of epiphyseal arrest, even simpler than that of Phemister, may yet be evolved.

Although late deformities have not been reported, we have encountered three patients operated upon according to Phemister's technic who developed disalignment at the knee sufficient to require operative correction. In experimental animals, attempts to arrest growth by his and other methods frequently resulted in severe lateral deformity. In a series of 25 rabbits, we were able to produce uniform and complete arrest of growth only when a considerable part of each side of the cartilage disk was removed and the remaining cells in this area destroyed by electrical cauterization. (Fig. 1.) With this combined procedure complete cessation of growth occurred either with or without the cortical graft across the epiphyseal line.

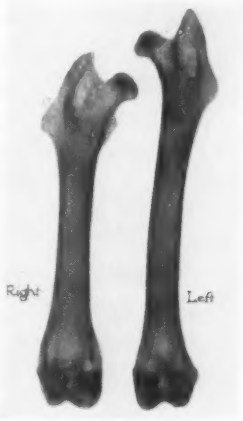

FIG. 1.—Rabbit bones after epiphyseal fusion on right, showing amount of shortening obtained.

At the Hospital for the Ruptured and Crippled, during the past four years, 34 operations for the retardation of growth have been performed upon 30 patients, with no infections and no postoperative deformities or other complications. The essential points of the technic are (Fig. 2):

(1) The medial and lateral sides of the lower end of the femur or upper end of the tibia and fibula are exposed through separate incisions.

(2) Bone grafts, about 1x4 cm. in size, are removed from the diaphysis. These extend as far as, but not across, the epiphyseal cartilage plate.

(3) A large area from both the medial and lateral aspects of the cartilage disk is removed with a chisel or curet.

(4) The curetted area is cauterized with the diathermy cautery.

(5) The grafts are replaced, countersunk beneath the cortex of the diaphysis, and driven across the epiphyseal line into the cancellous bone of the epiphysis.

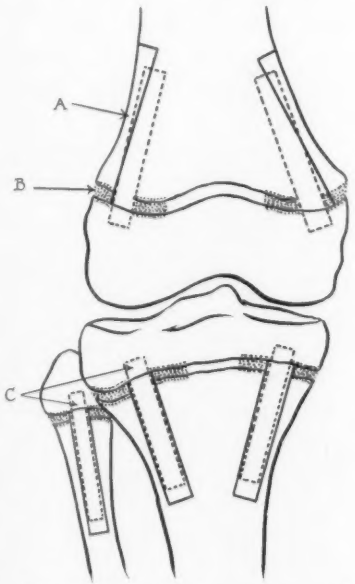

FIG. 2.—Diagram of operative technic for epiphysiodesis. (A) Bone removed for graft. (B) Area of epiphyseal cartilage curetted and cauterized. (C) Replacement of graft, with cartilage removed, across epiphyseal line.

More difficult than the actual technical procedure is the decision as to when the operation should be performed and which epiphyses should be fused. Digby,[30] in 1916, determined the proportional

growth at the various epiphyseal lines and his estimations have been confirmed by subsequent clinical observations. Complicated methods for determining the optimum age for operation have been propounded, based upon the average height, leg length, and growth rate at various ages. The authors feel that each patient must be considered individually and decision made upon the basis of previous rate of growth and expected growth in the extremities as well as age, height and leg lengths. Measurements of the patient's family are also of definite assistance. With these considerations in view, and the fact that practically all adults are between five and six feet in height, with a leg length of 30 to 38 inches, it is possible to arrive, with a fair degree of accuracy, at a figure which will represent the expected length of the longer extremity at maturity. Subtracting the present leg length from this figure gives the expected amount of growth in this leg if no treatment is undertaken. As attempts to estimate the growth in the femur and tibia separately only make the problem more complicated, the figures of Digby have been adjusted to apply to total leg length. For all practical purposes the figures shown in Table IV are sufficiently accurate.

TABLE IV

APPROXIMATE PROPORTIONAL GROWTH AT THE EPIPHYSES OF THE LOWER EXTREMITY

Upper femoral epiphysis	15%
Lower femoral epiphysis	35%
Upper tibial epiphysis	30%
Lower tibial epiphysis	20%

The expected discrepancy can be estimated if records of the leg lengths over a period of years are available. If the discrepancy has not been increasing with growth, the present discrepancy equals the expected discrepancy. If the rate of growth in the longer leg has been greater than in the shorter extremity, the discrepancy will continue to increase proportionately.

If the expected discrepancy is divided by the expected growth in the longer extremity, the proportion of growth which should be eliminated is obtained, thus $\frac{\text{expected discrepancy}}{\text{expected growth}} = \text{per cent of growth to be eliminated}$, for example—(1) If this proportion is less than 25 per cent, operative treatment should be delayed; (2) if it is between 25 and 60 per cent, growth should be arrested at the upper femoral or upper tibial and fibular epiphyses; (3) if it is more than 60 per cent, all the epiphyses at the knee should be fused; (4) if it is more than 70 per cent, complete equalization of leg length by this means cannot be obtained.

If the patient is under ten years of age the arrest of growth at a single epiphysis is preferred and is often sufficient. If the patient grows less than was anticipated and some discrepancy persists, another epiphysis can be fused a year or two later. If only a moderate retardation of growth seems indicated the decision as to whether the operation should be performed above or below the knee depends upon whether the shortening in the opposite extremity is greater in the thigh or lower leg.

It is impossible to report end-results in these cases until growth is complete, 14 patients, however, averaging 12½ years at the time of operation, have been observed from one to four years later. Seven of these showed a lessening in discrepancy of one to one and three-quarters inches. In three, the decrease was one-half to one inch. In two, the difference between the two legs remained the same, while in two, the discrepancy increased slightly despite the operation. Epiphyseal-diaphyseal fusion was accomplished in all cases, and even in those where no equalization of leg length was obtained a rapidly progressive discrepancy was arrested.

ILLUSTRATIVE CASE REPORTS

Case 1.—F. B., male, age 14. *Diagnosis:* Poliomyelitis in 1924, at the age of one year; resulting in a severe paralysis and marked shortening of the left leg.

Preoperative Measurements

Date	Age	R. Leg	L. Leg	Difference
3-6-29	5 yrs.	22 ins.	20¾ ins.	−1¼ ins.
12-5-34	10 yrs.	29¼ ins.	26¼ ins.	−3 ins.
2-5-35	11 yrs.	30 ins.	27 ins.	−3 ins.
3-8-37	13 yrs.	34¼ ins.	31¼ ins.	−3 ins.

Although the patient had already reached the age of 13, he was still growing rapidly, and as his family were also tall; the normal leg without treatment would probably grow three inches or even four inches more. If the present discrepancy of three inches is divided by the expected growth it is found that 75 to 100 per cent of this growth should be eliminated. On March 10, 1937, growth was arrested at the epiphyses of the lower end of the right femur and the upper end of the right tibia and fibula.

FIG. 3.—Case F. B. Views of knee 19 months after operative arrest of growth at the lower end of femur and upper end of tibia and fibula. During this period, the discrepancy in length decreased two and one-half inches.

Postoperative Measurements

Date	Age	R. Leg	L. Leg	Difference
9–15–37	13 yrs.	34¾ ins.	31½ ins.	−3¼ ins.
3–15–38	14 yrs.	34½ ins.	32½ ins.	−2 ins.
10–18–38	14 yrs.	35½ ins.	34½ ins.	−1 in.

After operation, the shorter leg grew three and one-quarter inches, while the longer one grew only one and one-quarter inches; showing that growth in the normal leg had been reduced at least 60 per cent.

Case 2.—J. M., female, age 12. *Diagnosis:* Poliomyelitis in 1927, at the age of one year; resulting in an extensive paralysis of the left leg.

Preoperative Measurements

Date	Age	R. Leg	L. Leg	Difference
9– 1–27	1 yr.	13⅜ ins.	13⅜ ins.	None
9–25–31	5 yrs.	20½ ins.	19 ins.	−1½ ins.
10–25–34	8 yrs.	27¼ ins.	25¼ ins.	−2 ins.
5–19–36	10 yrs.	28½ ins.	26½ ins.	−2 ins.

The patient's family were all rather short and although the patient was only age 10, she was well developed. It was evident that the normal leg without treatment would not grow more than six inches more. Dividing the discrepancy of two inches by the expected growth showed that at least 33 per cent of this should be eliminated. On May 20, 1936, an operation for arrest of growth was performed at the lower end of the right femur.

Postoperative Measurements

Date	Age	R. Leg	L. Leg	Difference
10– 2–36	10 yrs.	28¾ ins.	26¾ ins.	−2 ins.
2–26–37	11 yrs.	28¾ ins.	27¼ ins.	−1½ ins.
1–29–38	12 yrs.	30¼ ins.	29 ins.	−1¼ ins.

Although growth in the right leg had been retarded, there was still a discrepancy of one and one-quarter inches to be overcome. Operative fusion of the epiphyses of the upper end of the tibia and fibula was performed on February 16, 1938.

Postoperative Measurements

Date	Age	R. Leg	L. Leg	Difference
5 −1–38	12 yrs.	30¾ ins.	29½ ins.	−1¼ ins.
9–23–38	12 yrs.	31¼ ins.	30¼ ins.	−1 in.
12–30–38	13 yrs.	32 ins.	31½ ins.	− ½ in.

As a result of operations, the growth in the normal extremity has been reduced to three and one-half inches while the short, paralyzed leg was increasing five inches in length.

Review of the published reports and of our own cases leads us to conclude that destruction of the epiphyseal cartilage by operation at the lower end of the femur and/or the upper ends of the tibia and fibula is a simple and safe method of retarding growth. It is to be recommended as an effective means of equalizing leg length during the growing period.

II. Surgical Reconstruction.—(1) *Bone Lengthening Operations:* Codivilla was the first to devise a method for lengthening a long bone, as well as the first to employ the principle of direct skeletal traction. In 1905, he reported 22 cases, chiefly malunited fractures, in which he had performed an oblique osteotomy and applied traction by means of a pin inserted into the os

calcis. He had increased the length by from 3 to 8 cm. A firm anatomic foundation for bone lengthening was laid by Magnuson,[42] in 1908, when he reported the results of experiments in animals which demonstrated that operative lengthening of a normal extremity could be performed without interfering with the blood supply or nerve function.

Putti, in 1921,[51] reported a method for the operative lengthening of the femur, and was the first to make use of the principle of skeletal distraction. He first performed a long oblique osteotomy of the femoral shaft and then applied an apparatus consisting of two pins which were inserted from the lateral surface, one into the femoral condyles and the other into the greater

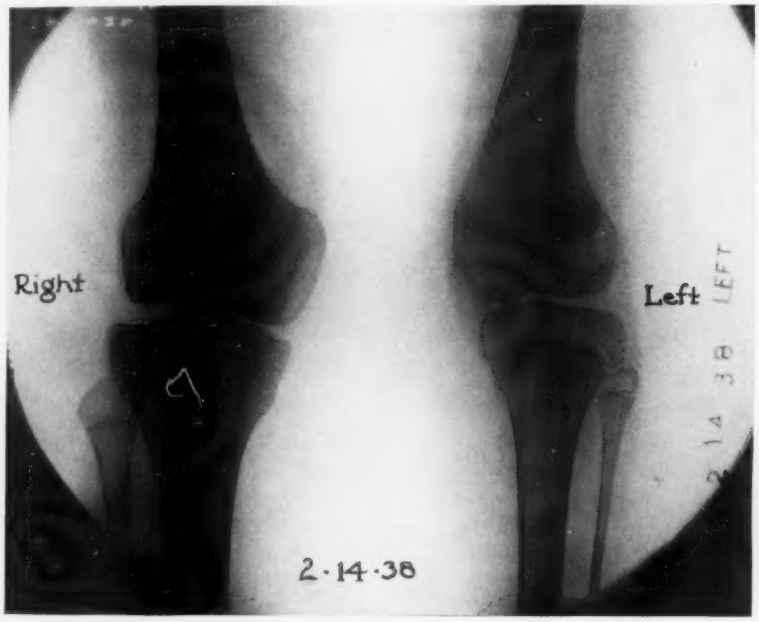

FIG. 4.—Case J. M. Roentgenogram taken 21 months after epiphysiodesis at right distal femoral epiphysis. Complete fusion has been obtained with three-fourths inch correction of discrepancy of length.

trochanter, and of a telescoping side-bar which was securely fastened to the protruding ends of the pins and could be gradually lengthened by turning up a screw-thread. Putti's method was tried by other surgeons but never became popular because of difficulty in controlling the alignment of the fragments.

It remained for L. C. Abbott[1] to devise a method which put leg lengthening on a practical basis. He selected the tibia and fibula as the ideal site for lengthening and after preliminary lengthening of the tendo achillis and oblique division of the shaft of the fibula, he performed a tongue and groove osteotomy of the shaft of the tibia, the tongue being long enough to overlap the other fragment after the desired lengthening had been obtained. Pins were passed through the upper and lower ends of the tibia and their projecting ends fixed to rigid, telescoping side-bars on both sides of the leg, the

apparatus when assembled forming a rigid unit and serving as a support for the extremity. Lengthening of approximately one-eighth of an inch a day was obtained by turning up screws until the desired amount was gained. Abbott published the first report of his method in 1927, and it was immediately adopted by other surgeons. He later modified it by employing four pins, two in each fragment to obtain better control of alignment. Other surgeons have devised ingenious modifications of his apparatus, but one and all have employed the same basic principles.

Lengthening of the femur presents more of a problem than that of the bones of the leg, owing chiefly to its deeper situation and stronger muscle attachments which make the control of alignment of the fragments after osteotomy more difficult. Abbott and Crego,[2] in 1928, described a method with one pin inserted through the condylar region and a second pin passed obliquely downward from the anteromesial aspect of the thigh through the upper third of the shaft and emerging at the posterolateral surface. By means of appropriate apparatus attached to the ends of the pins and also supporting the leg, lengthening was obtained gradually. This method proved too difficult, however, and never became popular. Modifications have been tried and femoral lengthenings are still undertaken, but their number in proportion to lengthenings of the lower leg is relatively small.

From this brief review it will be seen that more than ten years' experience with leg lengthening operations has accumulated, and a fairly accurate evaluation of the procedures can now be made.

A survey of the literature revealed reports by 11 different authors of their experience with leg lengthening operations. Of these, 224 were of the tibia and fibula and 46 of the femur. Lengthening was obtained in all but seven cases, regardless of complications. Average reported gains varied from 1.9 to 2.25 inches. The maximum amount gained from lengthening of one bone was 3.5 inches, but by combined lengthening of the femur and tibia in different stages, as much as 4.5 inches was obtained.

Numerous complications were reported and appeared to be of sufficient frequency and gravity to warrant careful consideration (Table V). Of these, the most disturbing was postoperative infection, which occurred in 22 out of 270 cases, an incidence of 8 per cent. Since several of the authors did not report their complications in detail, it is probable that this figure should be even higher. While it is impossible in this group of cases to separate the infections involving the site of osteotomy, and which were of major significance, from those that were confined to the pin wounds, of only local importance, it is evident that the former occurred entirely too frequently for comfort and are the natural consequences of a procedure that necessitates extensive exposure and traumatization of bone. It is important to point out, however, that only one death was reported in the entire series and aside from this case there were no amputations.

Without doubt, the tendency after tibial lengthening for the fragments to angulate anteriorly, and either protrude directly through the wound or cause necrosis of overlying skin with exposure of the bone, contributed to the high

TABLE V

REPORTED RESULTS OF LEG LENGTHENING OPERATIONS

Author	Number of Lengthening Operations		Average Length Gained (inches)	Complications Reported								
	Tibia and Fibula	Femur		Protrusion of Fragments or Skin Necrosis	Infection and Osteomyelitis	Delayed Union	Nonunion	Fracture	Nerve Injury	Foot Deformity	Death	Failure to Gain Length
Abbott	48	25			2			7	3	Many	0	
Stephenson and Durham	15	2		2	3					1		3
Carrell	21	7						2				
Brockway	41	5	1.9 ins.	5			1					
Janes	5		2.25 ins.		3				0	2		
Moore, J. R.	10				0	?			1		1	?
Compere		5			4	1	2			6		
Bosworth	19		1.9 ins.	2	2	3	4					4
Alcorn	37		1.5 to 2 ins.									
Haboush and Finkelstein	17			4	6	1	2			2		
Present report	11	2	1.9 ins.	5	2		3	1	1	3	0	0
Totals	224	46	2 ins.	18	22	5	12	10	5	14+	1	7

incidence of infection. This difficulty was encountered more frequently in the early experience and was largely overcome by the introduction of the four pin method.

Among the other complications reported were fracture of the osteotomy tongue in some instances of tibial lengthening, and separation of the fragments after femoral lengthening. These conditions resulted in delayed union when allowed to persist but were generally corrected by secondary operation with insertion of bone grafts to bridge gaps between the fragments and secure union. Callus formation and bone healing were delayed in some cases even when there was good approximation of fragments, and several instances of nonunion were reported for which bone grafting operations were necessary. Late fractures through the site of the healed osteotomy were not uncommon, as shown by Abbott's report of seven such complications out of 25 femoral lengthenings and occasional mention of similar experiences by other authors after tibial lengthening. Nonunion followed some of these fractures.

TABLE VI

LEG LENGTHENING OPERATIONS AT THE HOSPITAL FOR RUPTURED AND CRIPPLED

Case	Diagnosis	Shortening	Lengthening Obtained	Complications	Result at Last Visit
L. S.	Polio.	4 ins.	2¼ ins.	Tilting, projection of fragments, osteomyelitis, compound fracture, bone graft, refracture, amputation of leg	4 years later: Poor
E. W.	Old epiphysitis	1½ ins. Femur	1 in.	Tilting of fragments	Not known
P. M.	Polio.	1⅝ ins.	2¼ ins.	Slough, projection of fragments, osteomyelitis	3 years later: Poor
M. H.	Polio.	1½ ins.	Lengths equal	None	5 years later: Good
H. N.	Cong. shortening of femur	4 ins. Femur	1 in.	Secondary hemorrhage, infection, loss of peroneal nerve supply	4 years later: Paralysis persists
S. G.	Polio.	3 ins.	2½ ins.	None	4 years later: Fair
M. B.	Old epiphysitis	1¾ ins.	1⅜ ins.	Protrusion of tibial fragment through wound	7 years later: Good
P. D.	Polio.	2¾ ins.	2½ ins.	None	6 years later: Good
K. C.	Polio.	3¼ ins.	2 ins.	Slough, exposure of bone	3 years later: Fair
E. F.	Polio.	2¼ ins.	1 in.	Slough, protrusion of fragment	1½ years later: Fair
T. L.	Polio.	1¾ ins.	2½ ins.	Displaced epiphysis and overlengthened leg	3 years later: Good. Equal length
A. B.	Polio.	2 ins.	1½ ins.	Nonunion. Bone graft	4 years later: Good
A. M.	Polio.	3 ins.	2¾ ins.	Slight infection about pins	5 years later: Result good. Short leg ¼ in. longer

Other common complications were nerve paralysis and muscle contracture. The nerve most frequently injured was the common peroneal, giving rise to equinovarus deformity of the foot. Foot deformity was also frequently produced by uneven tension of muscles following elongation of the bones. The rigidity of some of these contractures was so great that some basis was afforded for the view that they might be of ischemic origin.

At the Hospital for the Ruptured and Crippled, 11 operations to lengthen the tibia and fibula were performed and two to lengthen the femur (Table VI). The results were considered good in six, with an average lengthening of two inches; fair in four; poor in two and unknown in one. The most common complication after tibial lengthening was anterior protrusion of the fragments, which led to exposure of the bone in six cases. There were two cases of nonunion of the tibia. Union was obtained in one, following a bone graft, but the other was complicated by bone infection, and when last seen this patient was still walking with a caliper brace.

That end-results of bone lengthening operations should not be judged too early is shown by the following case report:

Case Report.—L. S., white, male, age 22, was admitted to Hospital for the Ruptured and Crippled in January, 1934, with a history of poliomyelitis at the age of one year, with resulting weakness of the right lower extremity. Examination showed flexor power of the hip weak, extensor power fair, abduction absent; quadriceps muscles poor, biceps strong, but other hamstring muscles weak; very little power in the soleus-gastrocnemius group, tibialis posticus muscle weak; the other muscles controlling the foot good. There was a four inch shortening of the right leg and an operation to lengthen the lower leg was advised.

Operation.—February 1, 1934: Lengthening of tibia and fibula by the Abbott method and application of four pin extension apparatus.

Subsequent Course.—The patient made a good immediate recovery. The leg was gradually lengthened and by February 26, 1934, a gain of two and one-quarter inches had been obtained, which was considered sufficient. Six weeks after operation, a small area in the operative scar broke down and discharged a small amount of seropurulent material. The drainage quickly ceased; there was good callus formation and union seemed solid. The pins were removed and a plaster encasement applied. This was changed at the end of four months, at which time some drainage from the operative area was found and there was a small piece of bone exposed in the wound. The patient was discharged to the out-patient department on crutches with the leg in plaster. This was removed January 4, 1935, and a brace fitted. The wound was still draining and bone surface was exposed. Measurement showed the left leg only three-quarters of an inch longer than the right.

The patient was readmitted May 20, 1936, for muscle transplantations of the right thigh and hip, at which time the scar over the tibia was healed and there seemed to be firm union. He was still wearing a brace but chiefly for support of the knee. The operations were performed without event in two stages on May 22, and June 12, 1936, respectively. Each was followed by immobilization of the leg in plaster for a period of two to three weeks. The patient was discharged July 21, 1936.

October 3, 1936: Patient was readmitted because of a fracture of the right tibia sustained from a fall while playing football. The upper fragment of the fibula penetrated through the skin anteriorly. The wound was cleansed and dressed and a plaster encasement applied. Discharged November 4, 1936.

January 5, 1937: Readmitted because of pseudarthrosis of the right tibia. A massive onlay graft from left tibia was applied to right tibia and fixed with Sherman steel screws. Progress was uneventful and he was discharged March 23, 1937, with the leg in plaster, using crutches.

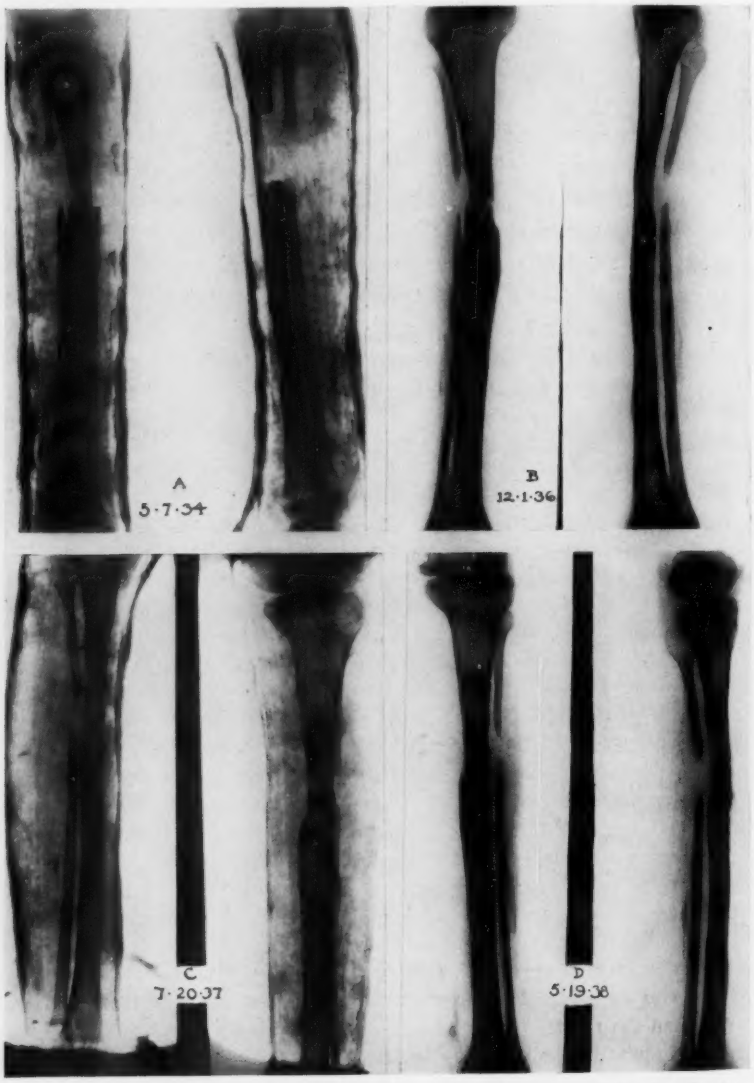

FIG. 5.—Case L. S. (A) Roentgenogram in plaster four months after lengthening operation. Two and one-fourth inches of lengthening obtained. (B) View taken ten months after original operation and two months after fracture from a fall. (C) Six months after massive onlay graft for nonunion of fracture. (D) Refracture of tibia following healing of previous nonunion, four years after lengthening operation.

July 20, 1937: Readmitted because of intertrochanteric fracture of right femur sustained by a fall while walking on crutches with his leg in plaster. The grafted area of the right tibia seemed solid. A plaster spica was applied. This was removed eight weeks after injury; roentgenologic examination showed good callus formation.

September 29, 1937, nine months after the bone grafting operation, the screws were removed from the right tibia as there was a small draining sinus in this area. He was discharged October 27, 1937, walking with a long caliper brace.

May 19, 1938: Readmitted because of a refracture of the right tibia sustained while turning in bed. There was still a small draining sinus. Since osteomyelitis was present and the tibia was sclerotic and thin, it was decided to amputate the leg. This was done May 25, 1938. He made a rapid recovery and was discharged.

August 15, 1938: An artificial leg was fitted and when last seen, December 10, 1938, he was walking quite well and was satisfied with his status.

SUMMARY.—We feel that bone lengthening operations, although feasible, are formidable procedures and should not be undertaken lightly. They necessitate prolonged hospitalization, and are frequently followed by serious complications which may still further impair the function of an already crippled leg. Previous infection of one of the bones of the leg to be lengthened should be considered an absolute contraindication, no matter how long it appears to have been healed. Failure to observe this rule may lead to disaster. Our survey showed that lengthening operations were performed more frequently for shortening resulting from poliomyelitis than from any other condition. Yet we believe that it is precisely in such cases that the results are likely to be the most unsatisfactory. Not only are partially paralyzed muscles apt to be still further weakened by stretching but the small atrophied bones are made still smaller and more brittle by elongation. The full consequences of bone lengthening operations under these conditions are not revealed except by prolonged follow-up studies.

From our observation and experience we believe that bone lengthening operations should not be performed until growth is well established, and then only when the musculature of the leg is normal or approximately normal. In general they should be reserved for individuals of short stature who are unwilling to make any sacrifice of height by shortening of the longer leg.

Leg Shortening Operations.—Shortening of the bones of the longer leg, in order to achieve equality of length, is a much older procedure than attempts to elongate the short leg by operation. Steindler credited Rizzoli with being the first to undertake this procedure. Sayre, in 1863, advocated fracturing the shaft of the femur and allowing the fragments to overlap the necessary amount. In 1908, Glaesseur reported three cases in which he had performed an oblique osteotomy and obtained sufficient overriding to overcome a discrepancy of leg length. Shands, in 1907, reported three similar cases. Brooke[16] was the first to report shortening of the lower leg. He described two successful cases in 1927, in which he had removed segments of bone one and two inches long, respectively, and applied inlay grafts, obtaining solid union in four months. He also reported shortening the femur by a step-cut method, with fixation of the fragments by two beef bone screws.

Camera[21] was the first to devise a standard method and to report any considerable series of cases. In 1933, he described his technic, which consisted of resecting a portion of the femoral shaft of the desired length, cutting this into a diamond-shaped peg, which was then used as an intramedullary graft

to fix the fragments together. The wide portion of the diamond served to prevent the graft from penetrating too far into either fragment. He reported a series of 32 cases. As complications, he cited two cases in which the fragments separated, necessitating reoperation and insertion of a metallic suture, three postoperative infections, and two cases of delayed union. The average period of external fixation of the limb was 50 days.

Moore,[45] also in 1933, reported a series of 13 femoral shortenings. He resected sufficient bone but left a spike projecting from the distal fragment that could be shoved up into the intramedullary canal of the proximal fragment for purposes of fixation. The average amount of shortening obtained was two and one-half inches, and the average period for complete union was two and one-half months. He reported no instances of infection, malunion or nonunion.

In 1935, White[60] reported a simplified method of femoral shortening, in which he performed a transverse osteotomy of the shaft, overlapped the fragments the necessary amount and fixed them together by inserting two long pins in an oblique direction upward and inward from the lateral side. The wound was closed with the ends of the pins protruding, which were incorporated in the plaster spica encasement. The pins were removed at the end of seven weeks, and the plaster encasement at the end of eight weeks. A caliper brace was then applied, and worn until the end of four months. He reported 47 cases treated by this method, their ages varying from eight to 42 years; the majority, however, were under age 14. The average amount of shortening obtained was two and one-half inches, with a maximum of three and one-eighth and a minimum of two inches. In the younger children, he shortened one-half an inch more than was necessary, in order to allow for continued disturbance of the growth rate, and expressed the wish that he had been even more radical. He encountered infection in four cases, with seropurulent discharge about the pin wounds, all of which cleared up in less than two weeks. Two ring sequestra separated from the pin wounds in another case and were extruded. Good functional results were obtained in all the cases.

At the Hospital for the Ruptured and Crippled, we have performed five femoral shortening operations according to the method of White. No complications were encountered, with the exception of one case in which pins made of a new type of steel were used and broke without, however, any loss of fixation. It was necessary to perform a later operation to remove the ends of the pins. An average shortening of two and one-eighth inches was obtained. To illustrate how much improvement in a patient's condition can be obtained by a combination of methods, the following case history is presented:

Case Report.—J. H., female, age 26, was admitted to the Hospital for the Ruptured and Crippled, May 5, 1937, with a history of infection of the right hip, probably tuberculous, at age 7. This resulted in ankylosis of the hip and failure of development of the right leg, so that for years she had walked with a limp and had to wear a lift, eight

inches high, under her shoe. She did not complain of any pain but was anxious to have something done to equalize the length of her legs so that she might discard her raised shoe.

Examination showed bony ankylosis of the right hip and an underdeveloped right leg. The hip was fixed in a position of 45° flexion and 15° adduction. The right knee

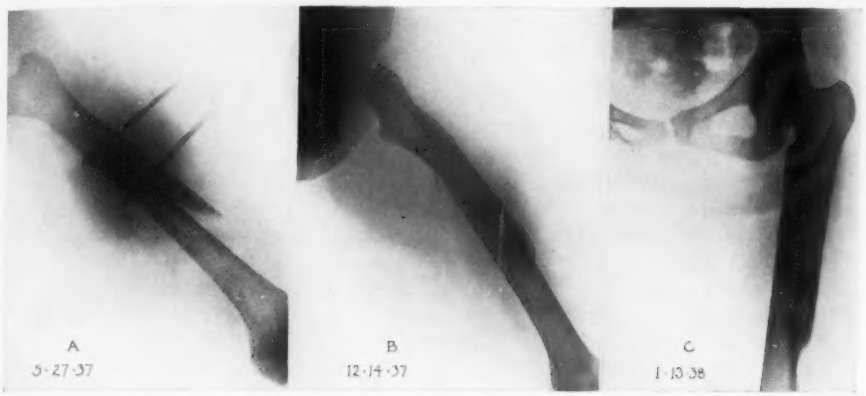

FIG. 6.—Case J. H. (A) Postoperative roentgenogram showing overlapping of fragments with three inches of shortening of femur and pins in place. (B) and (C) Views showing position and healing approximately eight months after operation.

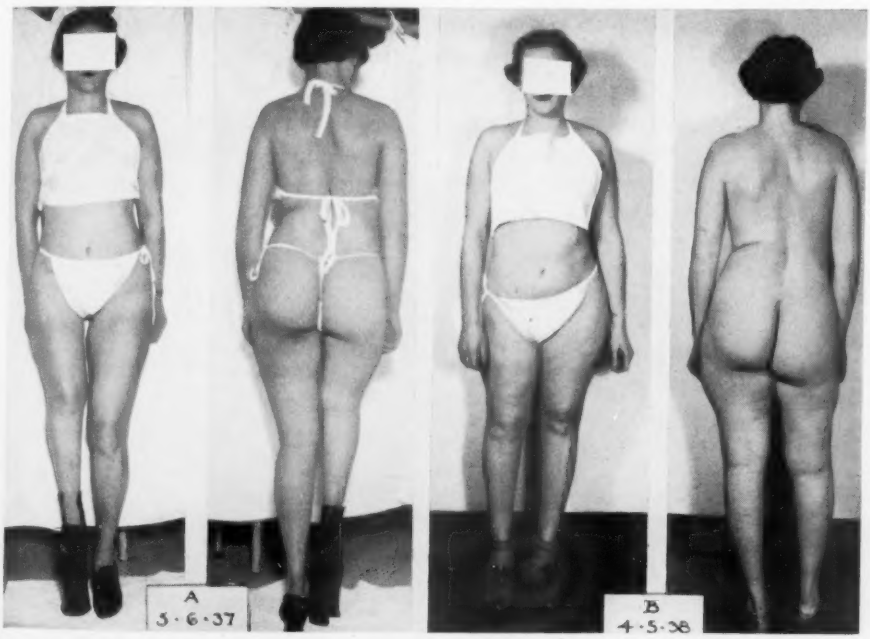

FIG. 7.—Case J. H. (A) Preoperative appearance of patient wearing eight inch lift on shoe. (B) Appearance after three inches of shortening of left femur, correction of adduction deformity of right hip and flexion deformity of right knee by osteotomies.

showed a normal range of flexion, but extension was limited at an angle of 165°. Measurements showed the length of the right leg 28½ inches, of the left leg 34½ inches, of the right femur 14 inches, and of the left femur 17½ inches. The flexed, adducted position of the right hip caused her to stand with marked lumbar lordosis

and with the right side of the pelvis raised so that there was a relative increase of the shortening. (See Figs. 6 and 7.)

First Operation.—May 8, 1937: Shortening of left femur by oblique osteotomy, overlapping of the fragments and pin fixation. Amount of shortening obtained, three inches. Application of plaster spica. Good postoperative recovery.

Second Operation.—May 24, 1937: Subtrochanteric osteotomy for correction of flexion and adduction deformity of the right hip. Plaster spica applied holding hip in position of 10° abduction and 15° flexion. Uneventful convalescence.

Third Operation.—June 21, 1937: Supracondylar osteotomy of right femur to overcome flexion deformity of right knee. Bilateral plaster spica.

Subsequent Course.—The patient did well. Union of the left femur and of the right hip appeared solid August 10, 1937, and the plaster was removed. A plaster leg encasement, to support the region of the right knee, was worn until August 31, 1937. She was then given exercise treatment in the pool, and weight bearing was permitted September 15, 1937. She was discharged one week later.

Patient was examined in the End-Result Clinic, October 18, 1938, at which time she stated that she was very pleased with the result. She walked well with a one-quarter inch lift under her right heel. The right hip was fixed in 10° abduction and 25° flexion. The right knee could be completely extended and flexed to an angle of 80°. The length of the legs, when measured from the anterior superior spine, was: right 29 inches, left 31¾ inches; when measured from the umbilicus: right 33½ inches, left 34¼ inches. The abducted position of the right hip was sufficient to cause enough relative lengthening of the leg nearly to compensate for the two and three-quarters of an inch actual shortening present.

SUMMARY.—We feel that leg shortening operations are practical procedures; that the technic varies with different surgeons, with the preference, however, either for the resection of a portion of the shaft with fixation by an intramedullary graft or for a simple overlapping operation with fixation by pins; that the complications are few and that the functional results are good (Table VII).

TABLE VII

REPORTED RESULTS OF LEG SHORTENING OPERATIONS

Author	Number of Shortening Operations		Average Shortening Obtained	Complications Reported				Results
	Femur	Tibia		Separation of Fragments. Reoperation	Infections	Delayed Union	Nonunion	
Brooke	1	2	1⅔ ins.	0	0	0	0	Good
Camera	32	0		2	3	2	0	Good
Moore	13	0	2½ ins.		0	0	0	Good
White	47	0	2½ ins.		4	0	0	Good
Present report	5	0	2⅛ ins.	0	0	0	0	Good
Totals	98	2	2 ins.	2	7	2	0	

There is a natural prejudice, both on the part of the surgeon and of the patient, against operating upon the normal leg when the other is already

crippled, but the results show that the method is justified when there is serious discrepancy in length and particularly when the shortening is confined to the femur. The maximum amount of shortening reported was three and one-eighth inches, but Hey Groves stated that the normal femur might be safely shortened by 25 per cent of its total length. As far as loss of muscle power resulting from the shortening is concerned, we can confirm the statement of Hey Groves that: "It is very remarkable how the slack of four inches of muscle is taken up within a few months and the full muscular power of the leg regained." We are of the opinion that leg shortening operations ought not to be performed until after growth has been well attained, both for fear that a continuing disturbed rate of growth may lead to later discrepancy in the length of the limbs and also because the resulting hyperemia may lead to an increased rate of growth on the shortened side, similar to that which has been observed following fracture of the femur. Either of these factors might upset the results of equalization.

INDICATIONS FOR, AND EVALUATION OF, THE DIFFERENT METHODS FOR EQUALIZING LEG LENGTH

The purpose of the authors in preparing this report was to compare the relative merits and disadvantages of the different methods of equalizing leg length (Table VIII).

TABLE VIII

COMPARISON OF METHODS OF EQUALIZATION OF LEG LENGTH

Method	Age	Period of Hospitalization	Seriousness of Procedure	Possible Correction
Local stimulation	3–14 yrs.	2 wks.	+	Slight
Lumbar sympathectomy	3–10 yrs.	3 wks.	+++	1 in.
Epiphyseal arrest	7–14 yrs.	3 wks.	++	4 ins.
Leg lengthening	over 14 yrs.	5 mos.+	++++	3 ins.
Leg shortening	over 15 yrs.	3 mos.+	+++	3 ins.

CONCLUSIONS

(1) Local stimulation of bone growth has not as yet been proved sufficiently successful to warrant clinical application.

(2) Lumbar sympathectomy, when indicated for the correction of circulatory disturbances in association with inequality of leg length, as frequently seen in poliomyelitis, may be expected to cause a favorable alteration of the diminished growth rate of the shorter extremity. Even when done before the age of nine years, improvement cannot be assured, and the greatest gain that can be expected is approximately one inch.

(3) Epiphyseal arrest in comparison with the other operative methods has the advantage of being a relatively minor surgical procedure. Few, if any, complications need be anticipated. Careful calculation is necessary to determine the age at which the operation should be performed, and which

epiphyses should be fused. This depends upon the age of the patient when first seen, the amount of shortening and whether or not it is increasing. When a gross discrepancy of length is to be overcome, the operation must be performed early. Complete fusion must be obtained in order to avoid any danger of later deformity due to asymmetric growth. This method offers the simplest and safest means of equalizing leg length. Its only drawback is that its application is limited to the growing period.

(4) Leg lengthening is a formidable procedure and frequently attended by serious complications. Until these difficulties have been overcome, its use should be limited to patients who are too old for epiphyseal arrest and are unwilling or ill able to sacrifice height by undergoing shortening of the longer extremity. Previous infection of a bone of the shorter extremity is a definite contraindication. We also warn against undertaking this procedure in a severely paralyzed or atrophic extremity.

(5) Leg shortening like epiphyseal arrest, has the disadvantage that it must be undertaken on the longer and usually normal leg. It is a relatively simple and safe procedure. Serious infection, nonunion, deformity and muscle weakness have not been reported. Although the operation has been performed almost exclusively upon the femur, it has also been undertaken successfully in the lower leg. The maximum correction so far reported is approximately three inches. Leg shortening should be advised only when growth is well established. Many patients show an aversion to loss of stature, but the elimination of the raised shoe more than compensates for this. Furthermore, it should be pointed out that a lowering of the center of gravity in a patient with a crippled lower extremity usually results in a gain of stability and an improvement of locomotion. Leg shortening, therefore, has the advantage over leg lengthening, in that it actually improves function.

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DISCUSSION—DR. CLAY RAY MURRAY (New York) said that Doctor Wilson and Doctor Thompson had presented one of the very best surveys of a difficult problem he had ever listened to. One of the most important features of the paper is that it did not stress so much the operative procedure

as the evaluation that every one of the cases presented had been put through before any operative procedure was attempted. Studies of the development of the child's background, familial growth, the particular stage of growth the child happened to be in (the very active growth that children go through, or one of the latent periods)—all were carefully evaluated before either operative procedure was undertaken or before the time for such procedure was chosen. Even if a method is ideally carried out, and despite the method used, without extremely careful and prolonged evaluation before carrying it out, its value may be very largely lost.

Dr. Alan De Forest Smith (New York) said that he had come to the same conclusions at the N. Y. Orthopedic Hospital as had Doctor Wilson, in evaluating the various methods of dealing with disturbance in the length of extremities. Leg lengthening is a very difficult and dangerous procedure, and fraught with many risks. It is reserved at the N. Y. Orthopedic Hospital for the very few cases in which the discrepancy is so great that it is impossible to overcome it by leg shortening.

Leg shortening is preferred in most cases by ephiphyseodesis in young children, before the end of their growth period, and by taking some bone out of the femur in adults and older children. Before dealing with this problem with entire success, it is necessary to have more data on the behavior of growth especially in poliomyelitis cases. Not enough is known about the effect of poliomyelitis on growth. From cases observed by Doctor Smith it is his opinion that they reach a stationary point at which there is no longer an inequality in rate, before the end of their growth period. A discrepancy in the growth of the extremities may result so that an extremity may lose an inch or two during a certain period of time. This difference then remains until the end of growth. If the behavior of these cases was more fully understood one would be better able to deal with them.

CLINICAL AND EXPERIMENTAL EXPERIENCES IN THE SURGICAL TREATMENT OF HYPERTENSION*

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IN 1935, one of us[1] (M. H. B.) reported his clinical experiences with and the mode of action of the sulphocyanates in the treatment of hypertension. It was found that if the oral dosage was adjusted until the cyanate content of the blood ranged between 6 and 12 mg. per 100 cc., a reduction of the blood pressure occurred in 35 of 45 patients with systolic blood pressures well over 200 Mm. of mercury. The blood pressure reduction was well maintained for months and even years in the individuals sensitive to this drug, if an average concentration of 10 mg. per 100 cc. of blood was held. It was emphasized that the dosage necessary to maintain a therapeutic concentration of the cyanates in the blood varies greatly, apparently due to the individual sensitivity and clearance of the mineral from the body. Since then, experience with a larger group of patients has been obtained, and these results have been corroborated.[2, 3]

The most striking effect produced by the cyanates is the drop of the systolic blood pressure. Decreases from 270 or 220 Mm. down to levels between 180 and 140 Mm. have been frequently produced and although the diastolic pressure usually lags some days or weeks, a reduction to levels of 80 to 100 Mm. may be obtained. The cardiac symptoms of heart consciousness, shortness of breath and nocturnal dyspnea usually decrease as the blood pressure falls and relief from headache, insomnia and nervousness often occurs even without the expected proportionate decrease in blood pressure. Compensation of the heart has generally followed, and is easily maintained, as long as the reduction of the blood pressure is held. A decrease of the size of the heart takes place in a few weeks, as may be shown by orthodiagrams and two meter roentgenograms. No damage to the concentration power of the kidneys nor retention of waste products has been encountered as the blood pressure has been reduced. At the same time, a fairly regular decrease in the red cell count, hematocrit, blood cholesterol and the total serum proteins has been observed if the cyanate therapy is continued and a proper blood cyanate level is held. The sedimentation rate is increased and there is an ease in drawing blood through a standard caliber needle, which suggests that the total blood viscosity is materially reduced.

In a series of over 200 cases, roughly 50 per cent have shown symptomatic improvement, with blood pressure reductions that are regarded as significant and satisfactory responses following cyanate therapy. In 25 per cent, an

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escape from the therapeutic effects of the drug occurs after a good initial response. In these latter patients, there is an enormous augmentation of the clearance of the drug, so that very much larger doses are required to maintain a satisfactory blood cyanate level. In the remainder, a gradual rise in blood pressure occurs in the face of a constantly maintained and seemingly adequate blood cyanate concentration, large enough in many instances to produce toxic symptoms. Of all the patients in this latter group, 50 per cent may be regarded as resistant to cyanate therapy.

For this group of cyanate resistant patients with hypertension, we have considered the possible advantages of surgical therapy. In a previous paper[4] we presented our criteria for choosing patients for the operation of bilateral supradiaphragmatic splanchnicectomy and set down the studies and observations which we carried out on each patient pre- and postoperatively.

(1) All patients have a severe grade of essential hypertension with a systolic pressure of 200 Mm. or over and with a diastolic pressure above 100 Mm. of mercury. (2) As far as can be detected by a careful history, physical examination and laboratory data, there is no evidence of chronic glomerular renal disease. (3) There is no evidence of significant peripheral arterial sclerosis. (4) Throughout their months or years of observations, blood pressures show normal fluctuations; that is, the pressures are not "frozen" at a definite level. (5) All of the patients have been given a thorough trial with potassium sulphocyanate over a period of several months up to two years. The sulphocyanates have been discontinued for one of two reasons; either the patient shows some response to cyanate therapy but the dose necessary to lower his blood pressure is large enough to cause symptoms of sulphocyanate intoxication, or he is not sensitive to the drug, particularly in regard to his diastolic blood pressure.

Briefly, then, relatively young hypertensive patients without renal damage whose blood pressures under normal conditions show rather marked fluctuations; whose vascular tree is still elastic, and who, over a long period of time for one of two reasons, have been found to be insensitive to potassium sulphocyanate therapy are subjected to critical study and observation before and after operation. These studies and observations consist of:

(1) Renal function tests of concentration and dilution power, urea clearance and fractional phenolsulphonphthalein excretion.

(2) Blood chemistry studies which include total serum protein, serum albumin and globulin, cholesterol, uric acid, blood and fluid volume, hematocrit, chlorides, CO_2 capacity, urea nitrogen, glucose and insulin tolerance.

(3) Blood pressures are taken morning and evening, during bed rest, for a period of four days and continued until a normal basal level has been reached. Blood pressure readings are then made while the patient is ambulatory; after meals; during periods of nervousness or excitement, and while asleep.

(4) The cold pressor test done according to the method described by Hines and Brown.

(5) A tablet of nitroglycerine (1/200 to 1/100 gr.) is placed under the tongue, and the drop in the pressure is recorded for a 20-minute period, or until the readings show that the pressure has returned to the average normal level.

(6) Changes in the blood pressure during a period of deep sleep induced by amytal, pentothal of sodium and avertin are recorded.

(7) Carbon dioxide inhalations are given to determine how high the blood pressure may be elevated under controlled conditions.

Clinical Experiences.—Recognizing from the outset that by limiting our choice of patients to those who had been proven to be cyanate resistant we necessarily were choosing difficult cases upon which to test the effect of a surgical procedure, we still were not quite prepared to meet the complete failures which attended our efforts in the first three patients operated upon.

Case 1.—D. G., female, age 29, was first aware that she had hypertension at age 24, in 1930. By 1932, she had edema of the ankles and had begun to tire easily at her work. The following year, she was forced to leave her position and was admitted to the Cardiovascular Clinic, complaining of severe headaches, dizziness, dyspnea, precordial pain, palpitation, insomnia and nocturia.

The blood pressure was 220/130 Mm. The heart was of normal size with only a moderately forceful apex impulse. The apical tones were muffled and there was a harsh rasping murmur occupying all of systole and diastole heard at the root of the neck on the right. The blood urea nitrogen was 13.4 mg., cholesterol 235 mg., blood chlorides 480 mg. and the phenolsulphonphthalein excretion test totalled 60 per cent in two hours. The left optic fundus showed edematous tissue about the vessels near the disk.

The patient was given 0.3 Gm. of potassium sulphocyanate twice daily and this dosage was gradually increased to learn her tolerance. During the next year she was out of the city at intervals and the blood cyanate level was difficult to control, but at no time did it ever exceed 6.9 mg. per 100 cc. of blood. Some of her symptoms were reduced, but none disappeared, and her blood pressure ranged near 220/100 Mm. From April, 1935, to July 1, 1935, the blood cyanate level was gradually raised to 19.3 mg., but her headaches, dizziness, dyspnea and other symptoms continued unchanged.

She was placed in the hospital and kept in bed for two weeks without cyanate therapy. Her blood pressure remained unchanged and her symptoms continued with even greater intensity. When her blood had become entirely free from cyanates her hematocrit reading was 41 per cent; total proteins 8.14 Gm.; albumin 4.95 Gm.; globulin 2.49 Gm.; urea nitrogen 13.5 mg.; uric acid 2.5 mg.; cholesterol 231 mg.; urea clearance 46 per cent; chlorides 440 mg. with a carbon dioxide capacity of 50.5 per cent.

On July 12, 1935, a bilateral supradiaphragmatic splanchnicectomy was performed and there was an immediate postoperative drop in the blood pressure to 154/90 Mm., but this lasted only three hours and quickly rose within seven hours to 180/114 Mm. An insulin tolerance test was performed several weeks later, and the patient had a violent hyperinsulin reaction after the injection of 10 units of insulin, quite characteristic of the reaction following section of the splanchnic nerve.

The patient's blood chemistry findings showed no essential change whatever upon several postoperative examinations, and although cyanates have been given at various intervals during the past three years following operation the blood pressure levels have never been critically lowered.

Quite convinced of the completeness of the operative procedure, we could only conclude that we had chosen a patient whose blood pressure levels

were frozen. We had not subjected this patient to any of the tests employed at other clinics in an effort to choose patients who might be expected to react favorably to an interruption of the splanchnic nerves. This, we believed, was an oversight which might have prevented us from subjecting the surgical procedure to a test far beyond its scope and so we approached the second case hoping that a favorable response to various tests for vascular lability might carry a more hopeful prognosis.

Case 2.—R. K. V. was refused an insurance policy in 1931, at the age of 34, because of a systolic blood pressure of 240 Mm. From 1933 until the fall of 1936, the patient was under medical management elsewhere, which succeeded in keeping his systolic pressure in the neighborhood of 150 Mm. He continued his work as a newspaper man and felt well. In October, 1936, he had bleeding from his left kidney and during hospitalization at that time his pressure had again risen to a systolic level of 240 Mm. From that time, to the time of his entrance into our clinic, he had complained of dyspnea, blurring of vision, severe headaches, precordial pain and a constant hematuria.

Upon examination February 13, 1937, the patient had a blood pressure of 266/166 Mm.; his fundi showed a bilateral papilledema with tortuous retinal arteries, hemorrhages and exudates. There was no cardiac enlargement but the peripheral vessels were tortuous and the pulse was bounding and not easily compressed. A cold pressor test and the nitroglycerine test caused no significant change in his blood pressure levels. Pentothal sodium (1 Gm.) was injected intravenously and although the systolic pressure fell while the patient was asleep it was not a marked change. During three weeks of absolute bed rest during which time potassium sulphocyanate was administered until the blood level was 12.7 mg. per 100 cc., there was no change in his blood pressure and his symptoms remained unchanged.

Previous to the administration of cyanates the patient's hematocrit reading was 41 per cent; blood urea nitrogen 19.4 mg.; cholesterol 368 mg.; chlorides 448 mg.; urea clearance 55.5 per cent; total protein 8.08 Gm.; albumin 3.06 Gm., and the carbon dioxide capacity 60.4 per cent. After the administration of the cyanates the hematocrit reading decreased to 39 per cent and the other blood chemistry determinations were essentially unchanged.

On March 22, 1937, a bilateral supradiaphragmatic splanchnicectomy was performed and although the immediate postoperative blood pressure was 154/110 Mm., within 24 hours it had risen to 195/130 Mm. and never fell below that level until his discharge on April 18, 1937, when it was 210/135 Mm. Again, an insulin injection of 10 units produced a typical shock reaction in this patient.

The patient's symptoms continued unchanged and there was so significant change in any of the blood chemistry determinations. The phenolsulphonphthalein excretion test was 64 per cent in two hours, practically the same as it was prior to operation, and the urea clearance test was not significantly altered.

The patient was discharged under the care of his own physician and succumbed within three months as the result of a cerebral vascular accident. During this time he had not been given sulphocyanates.

This second experience was even more discouraging than the results obtained in the first patient. Although his responses to the cold pressor, nitroglycerine and pentothal tests indicated a nonlabile vascular system, we felt that in view of the malignancy of his disease and his hopeless outlook, and our inability to place complete reliance upon the tests for vasomotor lability, he should be given the benefit of whatever advantages an operation might afford him. Thus far, in two patients we had not adhered to the

principles we had established for surgical indications and, in partial extenuation, had been unduly influenced by favorable reports in the literature. We were unable to satisfy ourselves that our cases were comparable in their clinical manifestations.

Certainly no changes had occurred in the various constituents of the blood. Likewise neither patient showed any improvement whatever in the subjective symptoms nor was there a change in the fundus findings following operation, both of which had been reported as a rather constant occurrence, irrespective of the effect upon the blood pressure.

We persisted in looking for a patient with severe hypertension, resistant to cyanate therapy, whose reactions to vasoconstrictor and vasodilator tests might give us encouragement. Finally, we believed that we had found one who might prove to be a less difficult problem; for, although she was resistant to the administration of cyanates, she exhibited prompt and marked reactions to the cold pressor, nitroglycerine and sodium pentothal tests.

Case 3.—F. M., female, age 38, was first aware of a hypertension in 1933, when she was age 34. She had suffered during the following four years with severe headaches, dyspnea, indigestion, fatigue, backache, and pain in her chest. Her blood pressure was 260/160 Mm.; the peripheral vessels were firm and there was a slight edema over the tibiae. The heart was enlarged to the left; the rhythm was regular and the tones were of moderate intensity with a systolic murmur at the apex and base. The optic disk margins were blurred bilaterally; the retinal vessels were small and there was a slight edema of the retinae.

The patient's blood pressure upon rest in bed was 182/108 Mm. and ten minutes after immersing her right arm in water at 40°C. for half a minute it had risen to 208/118 Mm. Two minutes after taking 1/100 gr. of nitroglycerine the pressure had decreased from 204/118 to 176/114 Mm.; six minutes later it had returned to 180/118 Mm. She felt after this test as if "all the blood was rushing to her head" and 15 minutes later complained of a terrific headache. Two minutes after starting the injection of 2 Gm. of sodium pentothal, her blood pressure dropped from 230/135 to 165/120 Mm. The injection was continued slowly for 15 minutes, during which the patient remained asleep and the blood pressure lowered. Thirty minutes after the injection had stopped the blood pressure had returned to 210/120 Mm.

On March 17, 1937, a bilateral supradiaphragmatic splanchnicectomy was performed, and a drop in the blood pressure was present for 12 hours immediately postoperative. Since that time, it has remained in the vicinity of the preoperative level although the patient's dyspnea and sense of chest constriction are greatly improved. The sodium pentothal test following operation showed a response exactly similar to that found before operation, as did the other tests for vascular lability.

This, then, was the third unsuccessful result we had encountered after sectioning the splanchnic nerves supradiaphragmatically. We had found no lead in a study of the blood chemistry before and after operation in two patients and finally we had been misled by responses to tests for vascular lability. Although all of these patients presented severe cases of essential hypertension and perhaps should never have been candidates for surgery because of the stage of their disease, we believed that similar patients had been operated upon elsewhere with an immediate drop in the blood pressure which had remained permanently lowered. Our only conclusions could be that either the operation

was ineffective or that we had chosen patients in whom the state of the disease was so far advanced that the operation should not have been expected to have been of help and that these patients were in no way comparable to those operated upon elsewhere.

During this period, Goldblatt and others had reported the production of hypertension experimentally in dogs, and had shown that even a total sympathectomy did not influence the hypertension which followed partial occlusion of the renal arteries. Although many operations had been performed upon patients, no physiologic explanation had been forthcoming to account for the clinical improvement observed in other clinics.

At this point, when we were convinced that the problem should be attacked from several angles in the experimental laboratory before we attempted the operation again in patients, we had an experience with a patient who had been under the care of one of us (M. H. B.) for many months. This individual (Mr. C. C. G.), age 39, presented all of the symptoms of a severe, essential hypertension with a systolic blood pressure ranging from 200 to 260 Mm. and a diastolic pressure of 120 to 140 Mm. He had been placed upon cyanate, and his blood cyanate level had been maintained for a number of weeks well above the average of 10 mg. per 100 cc. of blood, without any effect whatever upon his symptoms or blood pressure levels.

He had visited the Mayo Clinic in March, 1936, where his blood pressure was found to be 260/140 Mm. He had gone to that Clinic as a candidate for surgical treatment, but his responses to the tests employed there were such that he was not considered a suitable patient for operation. He returned to Chicago, and somewhat in desperation was again given cyanates, but this time his blood cyanate level was gradually raised to 20 mg. per 100 cc. of blood. Much to our surprise, his symptoms greatly improved and his blood pressure level was reduced to levels between 135 and 160 Mm. systolic and 100 and 120 Mm. diastolic. Mentally depressed, tired, and weak, he again returned to The Mayo Clinic where examination confirmed our impression that he was greatly improved except for the symptoms which could be ascribed to toxicity due to potassium sulphocyanate.

At this time (January 21, 1938), he was considered a suitable patient for operation and an infradiaphragmatic section of the splanchnic nerves, removal of the lumbar sympathetic ganglia, and a partial removal of the adrenal glands were performed. During his stay at The Mayo Clinic (until March 17, 1938) the lowest postoperative blood pressure reading was 150/110 Mm. By May, 1938, when he had returned to Chicago, however, his blood pressure had risen to 240/130 Mm., all of his previous symptoms had returned, and signs of cardiac decompensation were present. Again cyanates were administered and, again, to our surprise, his blood pressure was maintained at a level below 160/120 Mm. on a blood cyanate level of only 10 mg. per 100 cc. or less (Chart 1).

In other words, the patient had become sensitive to potassium sulphocyanate and he was clearing the drug efficiently, whereas prior to operation

he had been resistant and higher blood cyanate levels with the accompanying symptoms of mild cyanate intoxication had been necessary to reduce his blood pressure. Accompanying this reduction in blood pressure there had been a marked improvement in the patient's symptoms so that he was able to resume his former social and economic position, and there had been a definite improvement in his blood chemistry findings, evidenced by a drop in his blood cholesterol, total proteins and hematocrit readings.

Now, more than a year after operation, his blood pressure level is 175/100 Mm. with a blood sulphocyanate level of 12 to 14 mg., his symptoms remain improved and he is at work.

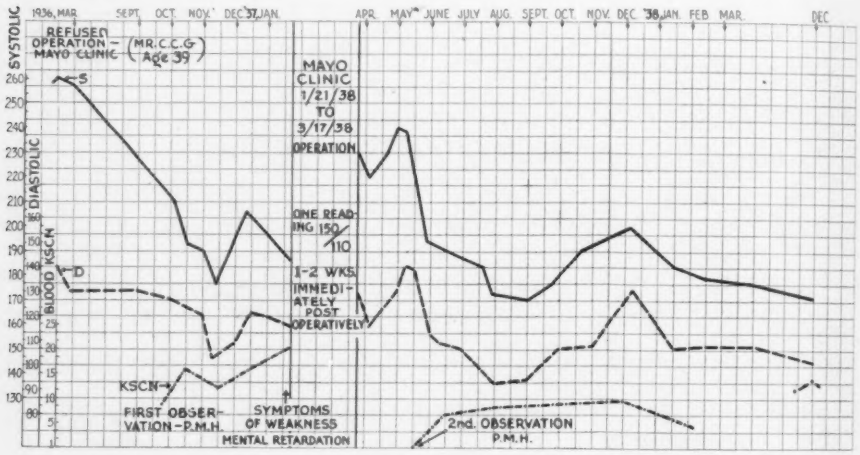

CHART 1.—Graph which shows the course of the blood pressure readings and the blood cyanate levels in patient C. C. G. before and following operation. Note also the blood pressure readings with the lower cyanate levels following operation.

We were quite unable to explain, physiologically, this improvement in the patient's ability to clear sulphocyanate more efficiently from his blood stream and to obtain the improved results from this drug. Nevertheless, it provided the encouraging stimulus to attack the problem anew both in the experimental laboratory and upon similar sulphocyanate resistant patients.

Our next patient was a schoolmistress whose hypertension, usually in the neighborhood of 200/130 Mm., was first noted in 1934, when she came under observation with the complaint that she had had frequent colds which kept her from her work.

Case 4.—E. M., female, age 32, was found to have a streptococcic infection of her nasopharynx. This was successfully treated, but in spite of a general improvement in her health she continued to complain of palpitation, throbbing of the vessels in her neck, attacks of dyspnea, occasional attacks of precordial pain, edema of the ankles and severe headaches. The cardiac borders were slightly enlarged to the left and the tones were accentuated but no murmur was present. There were no signs of decompensation. The optic fundi showed small retinal arteries, with thickened walls, blurred nasal borders of the optic nerve heads but no edema of the retinae.

The patient was placed upon sulphocyanate therapy, and it was found that if she remained in bed, her blood pressure could be reduced to 150/102 Mm. but upon resump-

tion of her normal duties the systolic and diastolic pressures immediately rose to levels of 200 and 130 Mm., respectively, and all of her symptoms returned. Pushing the sulphocyanate therapy to high levels, at which symptoms of weakness and mental retardation were present, failed to improve her condition as long as she attempted to maintain her economic position.

On June 29, 1937, a cold pressor test was performed. Placing the left arm in water at 32°C. increased the blood pressure from 176/132 to 200/136 Mm. in four minutes.

Nitroglycerine (1/100 gr.) beneath the tongue reduced the blood pressure from 192/134 to 172/130 Mm. in four minutes, accompanied by a bounding pulse, increase in the respirations and a sensation of weakness. Eighteen minutes after the nitroglycerine was given, the pressure level was 162/128 Mm. The blood pressure had returned to its former level at the end of 35 minutes.

One Gm. of sodium pentothal was injected slowly with the blood pressure level at 182/130 Mm. The lowest point reached by the blood pressure during her sleep was 152/110 Mm.

On July 1, 1937, the hematocrit reading was 43 per cent; urea nitrogen 15 mg.; uric acid 2.86 per cent; cholesterol 236 mg.; urea clearance 39.6 cc. or 73.2 per cent; total proteins 6.80 Gm. Ten units of insulin reduced the blood sugar from 85.2 to 63.0 mg. in three hours. The phenolsulphonphthalein test was 65 per cent.

On August 26, 1937, a bilateral supradiaphragmatic splanchnicectomy was performed, and although there was an immediate postoperative drop in the blood pressure levels, the preoperative state was reached within four days and remained so elevated until the time of her discharge September 20, 1938, when it was 180/130 Mm.

The cold pressor test was repeated September 17, 1937, and the pressure rose from 170/134 to 194/144 Mm. The nitroglycerine test was followed by a fall in the blood pressure levels from 180/134 to 168/128 Mm. At this time, ten units of insulin reduced the blood sugar fasting level from 39.0 mg., so that within an hour there was not enough sugar in the blood to be tested.

The blood chemistry determinations January 6, 1939, a year and one-half after her operation, showed a hematocrit reading of 40 per cent; total proteins 7.42 Gm.; cholesterol 258 mg.; chlorides 520 mg.; carbon dioxide capacity 50.4 per cent; urea clearance 67.1 per cent; blood urea nitrogen 17.2 mg.; phenolsulphonphthalein 40 per cent in 15 minutes. The cold pressor test showed a rise in blood pressure of 138/94 to 158/118 Mm. The nitroglycerine test produced no change whatever in the systolic or diastolic pressures. The sodium pentothal test showed a drop in the pressure from 138/94 to 110/80 Mm., and the carbon dioxide test showed a rise from 134/96 to 186/158 Mm.

Chart 2 shows the charted course of her blood pressure readings since September 12, 1934. Sulphocyanate therapy quickly produced a fall in the blood pressure, particularly when the patient was at rest, but when the blood was free from sulphocyanate the pressure rapidly rose. It was also noted that the blood sulphocyanate had to be raised to a higher level to effect the same result upon the blood pressure when she was at her work. Following splanchnicectomy her blood pressure is maintained at a constantly lower level upon small doses of potassium sulphocyanate while she is carrying on her normal daily duties, with blood sulphocyanate levels comparable to those which maintained the pressure at those levels when she was at bed rest prior to operation.

This patient afforded a confirmation of what we had suspected had occurred in the former patient. Observed as she was for three years before operation, during which time she had received cyanate therapy, her blood chemistry findings were more nearly normal than any of the patients we had studied previously. Her cholesterol was low and her hematocrit reading was fairly normal. On the other hand, her total blood proteins were elevated and her dye excretion and urea clearance tests were not the best. In other words,

one might argue that she was a more favorable patient for operation, if one did not remember that, although she responded to sulphocyanate therapy, it was only when she restricted her activities. The problem then was a practical one of attempting to make this patient economically independent. This has been accomplished by cyanate administration after splanchnicectomy, and during the past 18 months she has carried on her full duties as a teacher, by which she supports her mother and has done extra work in music, with a satisfactory blood pressure level. The patient's objective symptoms have all disappeared and recur only when she stops taking potassium sulphocyanate, as we have asked her to do several times to observe the subsequent rise in blood pressure.

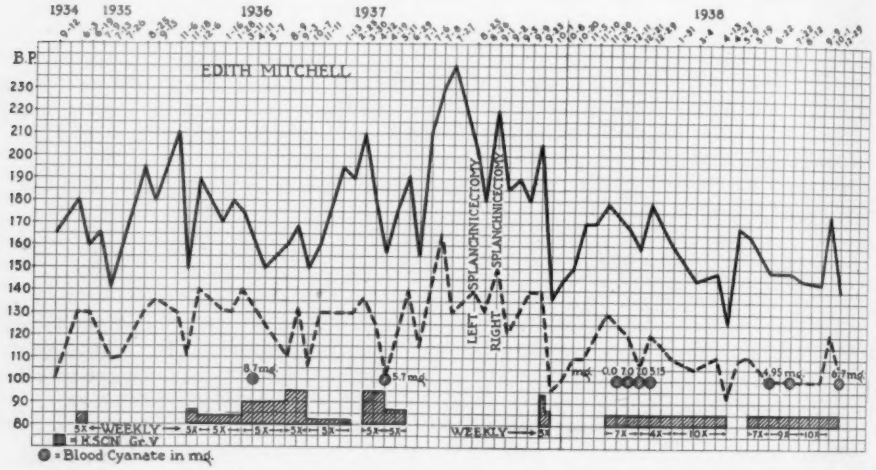

CHART 2.—Graph which shows the blood pressure readings and blood cyanate levels in patient E. M. from 1934 to January, 1939. The patient's blood pressure is definitely more responsive to smaller concentrations of cyanate in the blood following splanchnicectomy.

The excellent response of this patient stimulated us to investigate this particular phase of the problem further in other patients. As a result, we have centered all of our attention, clinically and experimentally, upon a specific phase of the surgical problem of hypertension, because in our hands, at least, it has been the only hopeful avenue of approach to the question.

The next patient was chosen for surgical treatment because, to our minds, he presented a difficult test to which we might put the idea that after splanchnicectomy the hypertensive patient would react more satisfactorily to the administration of potassium sulphocyanate. We had not been able to decide, from the observations made, whether or not less sulphocyanate was actually required to keep the blood pressure at a lower level or whether the drug produced its effect and was more rapidly cleared from the blood stream.

Case 5.—C. R., male, age 25, when first seen by one of us (M. H. B.), was in a deep coma and was having a series of convulsive seizures. He had been known to have a high blood pressure in 1931, and until December, 1935, had continued about his school duties although he complained of constant severe headaches. In February, 1936, he was taken to a hospital in coma, with severe vomiting and repeated convulsions. Potassium sulphocyanate was given intravenously with immediate cessation of the convulsions, re-

turn to consciousness and a decrease in his blood pressure levels from 260/160 to 170/120 Mm. This level was maintained successfully for 18 months, though toxic symptoms were present from time to time and close attention to the administration of the sulphocyanate was necessary.

Prior to consideration of a splanchnicectomy, the drug was stopped and his pressure rose while in the hospital to 230/150 Mm. The cold pressor test showed no change in the blood pressure level. On January 4, 1938, the hematocrit reading was 37 per cent; urea nitrogen 25 mg.; uric acid 4.15 mg.; cholesterol 260 mg.; chlorides 496 mg.; carbon dioxide capacity 55.3 per cent; total protein 5.58 Gm.; albumin 3.80 Gm. and globulin 1.78 Gm. The phenolsulphonphthalein test showed an excretion of 50 per cent of the dye.

On January 10, 1938, a left supradiaphragmatic splanchnicectomy was performed. The blood pressure dropped for a few hours after the operation but within 12 hours was 212/150 Mm.

On January 22, 1938, the patient began to complain of headache and dimness of vision. His blood pressure was 244/170 Mm. He soon became comatose and began to have a series of convulsive seizures; a clinical picture exactly similar to his condition in 1936. He was again given potassium sulphocyanate intravenously and in addition magnesium sulphate. His convulsions ceased, he became conscious and by January 25, his blood cyanate level was 4.25 mg. At that time, there was a bilateral edema of the optic disks but no marked engorgement of the retinal veins and there were no retinal hemorrhages.

It was decided that we could never free him from the drug because of the danger involved and consequently he was kept on sulphocyanate therapy until we sectioned the right splanchnic nerve on February 14, 1938.

Upon discharge from the hospital March 4, 1938, the hematocrit reading was 31 per cent; urea nitrogen 21.4 mg.; uric acid 2.0 mg.; cholesterol 240 mg.; chlorides 472 mg.; carbon dioxide capacity 70.5 per cent; urea clearance 48 per cent and the blood cyanate level was 11.8 mg.

The patient has been upon sulphocyanate therapy since, with a blood pressure level ranging around 170/110 Mm.; free from symptoms and physically active. On January 17, 1939, the hematocrit reading was 27 per cent; total proteins 5.71 Gm.; albumin 4.16 Gm.; globulin 1.55 Gm.; nonprotein nitrogen 48.5 mg.; blood urea nitrogen 34.9 mg.; uric acid 3.76 mg.; calcium 8.24 mg.; phosphorus 3.12 mg.; cholesterols 212 mg.; chlorides 552 mg.; carbon dioxide capacity 55.3 per cent; urea clearance 63.2 mg., or 84 per cent, and blood cyanates 26.6 mg. He has been carefully followed now for one year following his operation and his improvement remains while he follows a normal active life (Chart 3).

The necessity for keeping this patient upon potassium sulphocyanate therapy during the time we were attempting to determine the effect of splanchnicectomy made it impossible to draw any conclusions from the blood chemistry findings or other tests after the operation. During this past year, following splanchnicectomy, the patient has shown an increased sensitivity to sulphocyanate and although his blood cyanate level must be kept at a comparatively high concentration his reactions to the drug have been less and his condition therefore far more satisfactory. It would be difficult to attribute this change in the patient's response to the drug to some unknown factor inherent in the course of his disease and we believe that it can more logically be said to follow section of his splanchnic nerves.

The last patient to whom we wish to direct attention in this communication, has shown the same excellent response recorded in the patient E. M.

(Case 4). Most striking, has been the manner in which the total proteins in the blood, and particularly the globulin fraction, have fallen after her operation. Previous to operation, though a high level of blood cyanate concentration was reached without the production of toxic symptoms, neither her blood pressure levels nor her blood chemistry findings showed any of the changes so characteristic of the results obtained in patients who respond favorably to cyanate administration.

Case 6.—N. F., female, age 43, married, had been under close observation for 18 months, during which time she had been kept at bed rest in the hospital for 60 days. In June, 1937, she was first told that she had a high blood pressure. Her complaints were weakness, nervousness, nausea, headaches, edema of the ankles and blurring of vision.

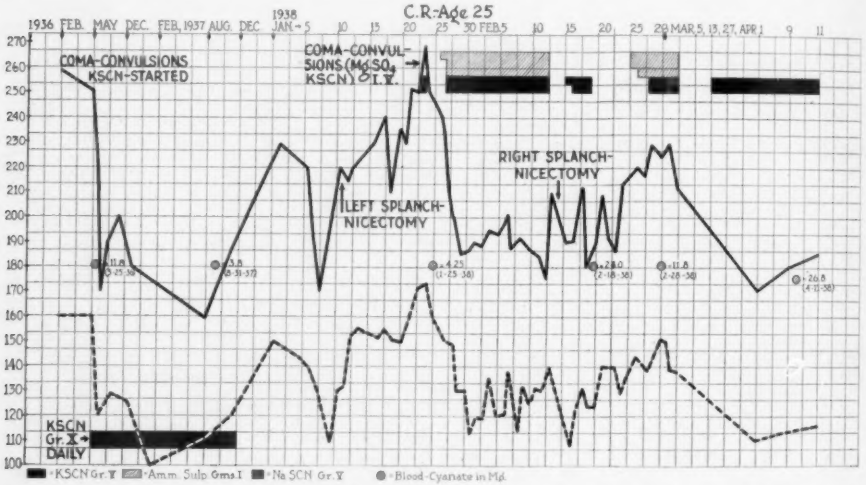
C.R.-Age 25
1936 FEB. MAY DEC. FEB. 1937 AUG. DEC. 1938 JAN. FEB. MAR. APR.
COMA-CONVULSIONS KSCN-STARTED
COMA-CONVULSIONS ($MgSO_4$ KSCN) & I.V.
RIGHT SPLANCHNICECTOMY
LEFT SPLANCHNICECTOMY
KSCN Gr. X DAILY
KSCN Gr. X
Amm. Sulp. Grms. I
Na SCN Gr. X
Blood-Cyanate in Mg.

CHART 3.—Graph which shows the effect of potassium sulphocyanate given intravenously in patient C. R. who was in coma and was having convulsions in 1936. All the cyanates were withdrawn and a left splanchnicectomy was done. The patient's blood pressure rose rapidly, the patient became comatose and developed convulsions so that potassium sulphocyanate was again given intravenously. A right splanchnicectomy was done later but the cyanates were continued. This patient requires large doses of cyanates to keep his blood pressure low but shows none of the toxic symptoms which developed from high concentrations of the drug in the blood before operation.

Ophthalmoscopic examination revealed arterial spasm with irregularity in the size of the vessels and blurring of the disk margins. The heart borders were not enlarged and there was no evidence of cardiac decompensation. While under observation in the hospital previously, her blood pressure levels had ranged from 260/163 to 140/88 Mm. and at entrance, June 27, 1938, the blood pressure was 192/108 Mm.

On January 5, 1938, the hematocrit reading was 45 per cent; urea nitrogen 11.4 mg.; uric acid 4.05 mg.; cholesterol 288 mg.; chlorides 495 mg.; carbon dioxide capacity 54.1 per cent; urine urea 236 mg.; urea clearance 30.1 per cent; total proteins 7.35 Gm.; albumin 4.21 Gm.; globulin 3.09 Gm.

The average resting blood pressure was 193/107 Mm.; the cold pressor test was followed by a rise of 38 points in the systolic pressure and six points in the diastolic pressure. Sodium pentothal was given with the control pressure at 210/115 Mm., and during the sleep so induced the mean pressure was 172/109 Mm., the lowest pressure recorded being 156/106 Mm.

On July 1, 1938, a bilateral supradiaphragmatic splanchnicectomy was performed and following this the blood pressure fell precipitately but then gradually rose to 170/96 Mm. on the second postoperative day. On July 5, the blood pressure was found to be 230/130

Mm., though, in general, the mean blood pressure readings were consistently lower. Postoperatively, the cold pressor test showed a sharp rise from 190/100 to 230/110 Mm. and a prompt fall to 180/96 Mm. The sodium pentothal test following operation produced a fall of the systolic pressure from 180 to 160 Mm. three hours after the administration of the drug and then a gradual return after eight hours to 170 Mm. The diastolic pressure on the other hand fell from 106 to 90 Mm. after three hours and continued to fall gradually to 76 Mm. eight hours after the test, after which it gradually rose again.

On July 18, 1938, when her blood was free from cyanates, the hematocrit reading was 41 per cent; urea nitrogen had risen to 28.3 mg.; uric acid was 5.25 mg.; cholesterol 248 mg.; chlorides 521 mg.; carbon dioxide capacity 50 per cent; urine urea 395 mg.; urea clearance 22.9 per cent; total proteins 7.03 Gm.; albumin 4.20 Gm. and globulin 2.83 Gm.

The patient's headaches had disappeared entirely, as had her nervousness, nausea and feeling of fatigue. In general, her subjective symptoms were greatly improved, a fact which has been noted and commented upon generally by all workers irrespective of the type of operation performed.

It was found necessary, however, to begin the administration of potassium sulphocyanate, because the blood pressure levels had risen and the patient's symptoms began to return as she became active about her house. The response to the drug, however, was prompt and effective. Eight months following operation, the patient's general condition has greatly improved and she is carrying on her daily household duties without any complaints. Her blood pressure levels are in the neighborhood of 170/100 Mm. on small doses of potassium sulphocyanate, which keep her blood cyanate levels at an average of 12 mg. without any evidence of toxic symptoms.

The blood chemistry determination January 6, 1939, showed hematocrit reading 42 per cent; total proteins 6.65 Gm.; cholesterol 263 mg.; chlorides 538 mg.; carbon dioxide capacity 47.7 per cent; urea clearance 39.7 per cent; blood urea nitrogen 22.9 mg.; phenolsulphonphthalein 10 per cent in 15 minutes. The cold pressor test showed a rise from 162/106 to 184/114 Mm. The nitroglycerin test showed a fall from 128/72 to 114/72 Mm. The sodium pentothal showed a drop from 140/94 to 120/84 Mm.

Whereas, prior to operation there was hypertrophy of the left heart as compared with the right, six months postoperatively, the size of the heart was within the upper limits of normal and the left side was still slightly larger than the right.

This patient then had not shown a drop in the total proteins of the blood upon sulphocyanate administration before the splanchnic nerves had been sectioned; a response which, after experience, we have learned to expect when the patient responds successfully to the drug. On the other hand, following operation, upon sulphocyanate therapy, there has been a definite response (Chart 4). Moreover, this patient alone showed a more profound reaction to the administration of sodium pentothal following operation, characterized particularly by the drop in the diastolic pressure. As we have pointed out before, we believe that the drop in the diastolic pressure is the important factor to be considered in evaluating any effect produced by drugs or operation upon the blood pressure levels.

Experimental Experiences.—From the beginning of our interest in this problem, we have carried on experiments in the surgical laboratory in an attempt to duplicate the results on animals and to attempt, if possible, to devise experimental methods which might help us determine how potassium sulphocyanate produces its effect and how section of the splanchnic nerves influences that action.

We chose Goldblatt's method of producing an ischemia of the kidneys by

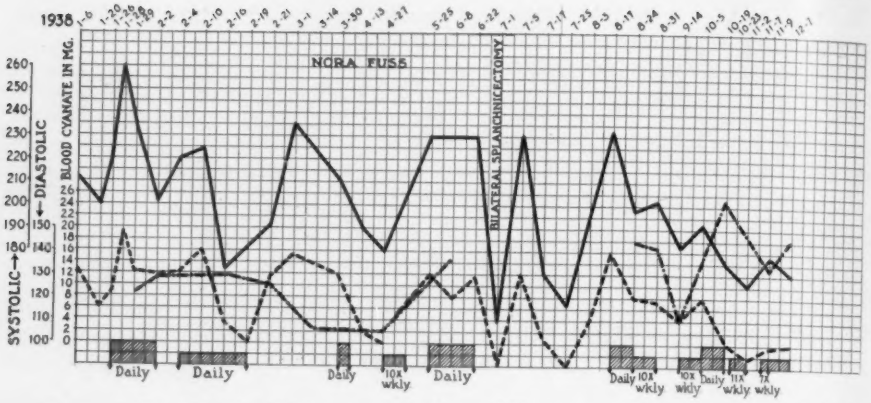

CHART 4.—Graph showing blood pressure readings and blood cyanate levels in patient N. F. before and after bilateral splanchnicectomy. While the patient was not as resistant to the cyanates before operation as other patients, following operation her blood pressure can be kept at a low level on small doses of cyanates without any danger of toxic symptoms.

placing a clamp on the renal arteries, as the most satisfactory method of producing a hypertension in dogs, which in our opinion simulated hypertension in man as closely as was experimentally possible.

Lindberg, Wald and Barker[5] showed that upon administration of sulphocyanates to normal dogs there was a prompt fall in the blood cholesterol value

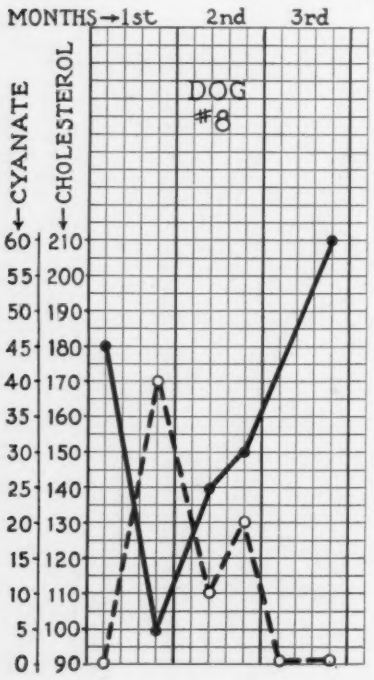

CHART 5.—Graph which shows the action of the cyanates (broken line) upon the cholesterols (solid line) in the blood in a normal dog.

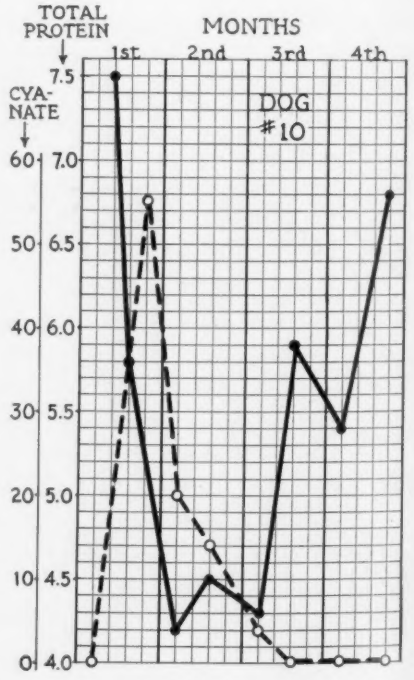

CHART 6.—Graph which shows the effect of the cyanates (broken line) on the total proteins of a hypertensive dog (solid line).

and that there is a definite parallel between the elevation of the blood thiocyanate level and depression of the blood cholesterols (Chart 5). Clinically, the response of the blood proteins resembles, in most respects, that of the blood cholesterol (Chart 6). In the presence of this depression of blood protein, either the albumin or the globulin fraction may be more profoundly affected, or both may be equally reduced. Clinically, a depression of the globulin portion with therapeutic doses of the drug has been observed but experimentally, with toxic doses of the drug in dogs there is a proportionate suppression of both the albumin and globulin portions. The fall in the erythrocyte count and the hematocrit in the blood of the dogs was striking. The gradient is in most cases very gradual particularly during the period of administration. Following cessation of administration of the drug, there is a slowing of the fall in the red cell count or an actual cessation of the fall. The hematocrit, which shows a much wider response, tends to stabilize more quickly after the blood is cleared of potassium sulphocyanate.

The livers of dogs fed excessive doses of inorganic sulphocyanate salts show intracellular fatty vacuolization to a marked degree. These changes involve the parenchymal cells, which show practically no tendency toward regeneration or compensatory hyperplasia. Jaundice does not accompany this hepatic degeneration, and although there have been too few opportunities to study the effect of the cyanates upon human tissues, the changes in the blood cholesterol and total protein suggest definite functional hepatic changes.

Bone marrow sections from rib, sternum and femur show a relatively acellular structure. In the least severely intoxicated animals, the normal matrix was replaced by fat but as toxicity became more severe the fatty marrow was replaced by a clear, light, eosin-staining gelatinous material.

Anatomic changes in the adrenal glands were not found in these experiments and chemical analyses of the blood with special reference to sugar metabolism, sodium, potassium and chloride failed to indicate any depression of the function of the adrenal gland.

We have been able to show in every experimental hypertensive dog that administration of potassium sulphocyanate is followed immediately by a drop in the mean arterial pressure. In the hypertensive dog, the hematocrit reading rises, as do the total proteins, blood urea nitrogen and cholesterols in the blood. Following the drop in blood pressure after administration of sulphocyanate there is a parallel drop in the hematocrit, total proteins, cholesterol and blood urea nitrogen. This is well illustrated in the case of "Point," a male, German police dog, and has been confirmed in 10 other animals (Chart 7).

In a group of six dogs, in which the blood pressure level was decreased by the administration of sulphocyanate, bilateral section of the splanchnic nerves supradiaphragmatically was performed after the animals' blood had been freed from the drug. In general, we have observed falls in the blood pressure levels following the operation which have been comparatively more marked and longer maintained than in man, but in every instance there has been a return

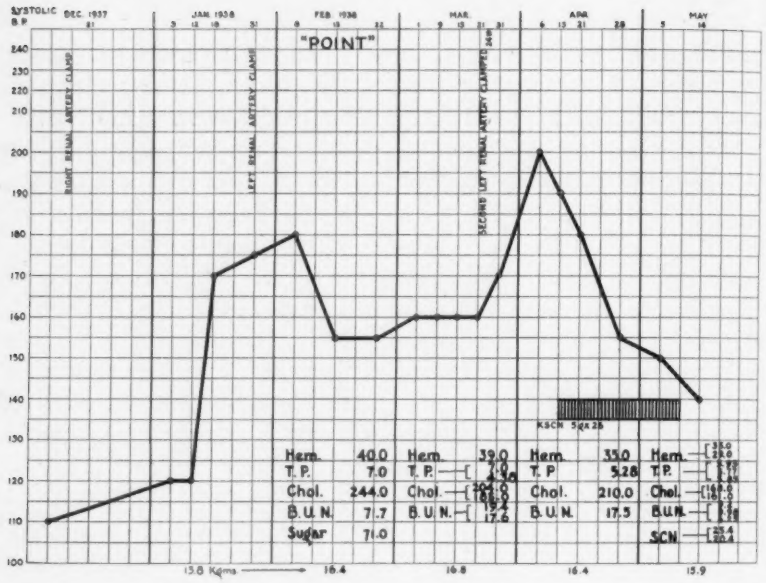

CHART 7.—Graph which shows the mean arterial pressure in hypertensive dog "Point" and the effect of cyanate therapy upon the arterial pressure and the blood chemistry findings. Note the decrease in the total proteins and the cholesterols.

to the original hypertensive level. Potassium sulphocyanate was then administered postoperatively with a similar hypotensive response to the drug (Chart 8).

We are unable to say that, in our experimental hypertensive animals following splanchnicectomy, there is an increased sensitivity to the cyanates, be-

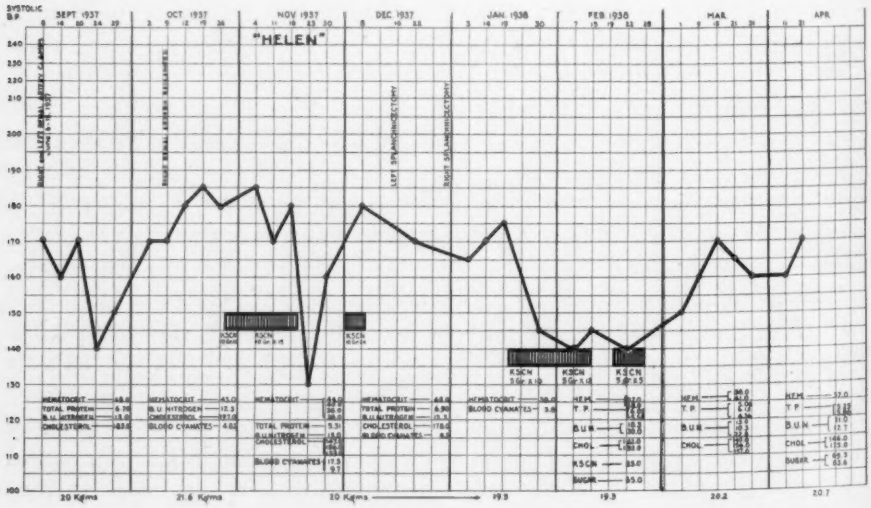

CHART 8.—Graph showing the mean arterial pressure in hypertensive dog "Helen" and the effect of cyanates upon the pressure and blood chemistry findings before and after bilateral splanchnicectomy. Note the lowering of the hematocrit, total protein, and cholesterol readings. There is some reason to believe that following splanchnicectomy the mean arterial pressure is more sensitive to smaller doses of cyanates in such an animal.

cause every hypertensive animal reacted promptly and effectively to the drug prior to operation. Some of these animals have been hypertensive for 12 to 18 months without becoming resistant to the drug. We have attempted to compare the blood cyanate levels and the drops in blood pressure before and after operation to determine if possible a quantitative difference but thus far have obtained only suggestive data which are insufficient for definite conclusions to be drawn. We are now observing a series of hypertensive animals over an even longer period of time in an effort to see if we can produce an animal which becomes resistant to the effect of the cyanates and is, therefore, more analogous to the patients we have observed.

SUMMARY

We have found that the majority of hypertensive patients observed by us respond favorably to the administration of potassium sulphocyanate as evidenced by a drop in the systolic and diastolic blood pressures, a fall in the blood cholesterols, total proteins, and hematocrit reading; relief from the symptoms of headache, insomnia, nervousness, fatigue, dyspnea, heart consciousness and actual decrease in the size of the heart. However, there is a small group of patients who are resistant to sulphocyanate therapy. The drug must be pushed to the toxic level in these individuals before any effect can be obtained and the lack of a safe margin makes it impossible to successfully control symptoms or blood pressure.

In our experience with these patients, bilateral section of the splanchnic nerves supradiaphragmatically alone has failed to decrease their blood pressure levels or have any effect upon their blood chemistry findings. After this operation, however, we have found that in four patients there has occurred a response to the administration of sulphocyanate which was not present preoperatively. Three additional patients have been operated upon but the time interval following operation has been too short to justify the inclusion of their data. The blood pressure, systolic and diastolic, has shown a definite drop and there has been a decided improvement in the disturbing symptoms of which the patients complained. At the same time, there has been a parallel decrease in the blood cholesterol, total protein, urea nitrogen and hematocrit readings which compares favorably with the same responses obtained in patients with hypertension who are sensitive to the sulphocyanates.

We think that we have had a sufficient experience to justify our belief that section of the splanchnic nerves has, in some manner as yet unknown to us, increased the sensitivity of a small number of patients to sulphocyanates. It might be suggested that as a result of the vasodilatation produce by splanchnicectomy, the patient clears the mineral from his body more effectively and thus, that higher concentrations of cyanates in the blood are possible without the production of toxic symptoms. Or, it may be argued as equally true, that the resultant vasodilatation of the viscera allows sulphocyanate to act more effectively. This is a matter about which we need more data than are avail-

able at present and it should come from the combined experiences of more than one group of workers.

We can say that our successful results have occurred in the patients who have shown definite responses to tests designed to evaluate objectively the lability of the patient's vasomotor responses. The accumulation of these facts upon a large group of patients from many sources will help answer this question of the value of these tests for operability with finality.

We have been able to duplicate the usual blood chemistry findings present in man with hypertension in dogs in which an experimental hypertension has been produced by renal ischemia. We have been able to reduce the mean arterial blood pressure, the total serum proteins, cholesterol in the blood and the hematocrit reading by the administration of the cyanates. We have not observed a permanent change in the blood pressure level or the blood chemistry findings of these hypertensive dogs after bilateral section of the splanchnic nerves supradiaphragmatically; but the effect of this operation in these animals has been more striking and is maintained longer than in the patients we have studied. We have only suggestive data thus far that in the experimental animals, there is an increased sensitivity to potassium sulphocyanate following splanchnicectomy.

Finally, the mechanism of the action of sulphocyanate still remains to be explained. Westphal and Blum[6] have suggested that the increase in the blood cholesterols in hypertension causes decreased permeability of the arteriolar muscle cells. They have suggested that sulphocyanate increases this permeability; that the arteriolar portion of the vascular bed relaxes and the arterial blood pressure is thus reduced. It is just as possible that sulphocyanate acts directly upon a pressor substance to modify its effects, or that the drug acts upon glands of internal secretion or their hormones through which the pressor substance acts. Or, it is possible that the hypotensive effect of the cyanates is purely incidental to their more general toxic effects. Vascular relaxation may be simply a part of the depressing effect upon the liver, bone marrow, central nervous system or glands of internal secretion.

Neither our clinical nor our experimental experiences with the problem of hypertension allow us to make any definite statements as yet as to the exact mode or site of action of potassium sulphocyanate in patients with hypertension.

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DISCUSSION.—DR. MAX M. PEET (Ann Arbor, Mich.): I was particularly impressed in Doctor Davis' communication with the fact that hypertensive dogs—hypertensive because of the Goldblatt clamp—did respond to potassium sulphocyanate. The idea of the splanchnicectomy, at least as we do it, is to increase the blood supply to the kidney. We believe that in hypertensive patients there is a theoretical Goldblatt clamp—in other words, a continuous vasomotor spasm of the renal vessels. The idea of the operation is to remove this neurogenic clamp.

The fact that Doctor Davis' dogs with the clamp in place do respond to potassium sulphocyanate shows that the action of the potassium sulphocyanate is not due to an increase in the blood supply to the kidney. It must be from some other action.

In our medical clinic, sulphocyanates have been employed to a more limited extent perhaps than anywhere else, because our men have not been at all enthusiastic with the results obtained. So the series that we have operated upon has not been cases proved definitely to be resistant to sulphocyanate.

I am very glad Doctor Davis has limited his cases for operation to that particular group, because through such special studies we may finally obtain a definite knowledge of the whole subject.

Tables I, II and III show the results we have obtained in supradiaphragmatic splanchnicectomy in patients who are not sulphocyanate resistant.

Table I shows all patients whose preoperative blood pressures averaged over 200 systolic and over 100 diastolic. Immediate postoperative blood pressure records have little significance. Therefore, all the readings included in this study were made at least six months after operation. The longest postoperative period is five years. A great many of them belonged in the so-called malignant stage, that is, they had hemorrhages in the eyes, exudates, and a great many of them showed edema either of the retina or of the optic disks. The age group, as you will see, is certainly very important. There is only one, a girl, age 16, in the 10 to 20 group; but in the 20 to 30 group, there were 17 patients; 13, or 76 per cent, showed definite improvement in blood pressure. Even in the age group of 50 to 60, 40 per cent showed a material reduction in blood pressure. We established the following standard: A reduction in blood pressure, averaged from many readings, must be over 40 Mm. systolic and 15 Mm. diastolic to be considered significant.

TABLE I

AGE DISTRIBUTION OF 90 PATIENTS WITH SIGNIFICANT REDUCTION IN BLOOD PRESSURE OF A TOTAL OF 194 CASES. FOLLOW-UP FROM SIX MONTHS TO FIVE YEARS

Age	Total Cases	Improved	Per Cent
10–20	1	1	100
20–30	17	13	76.5
30–40	54	24	44.5
40–50	92	42	45.7
50–60	30	12	40

The question has been raised, "How permanent is this result?" None of the statistics in Table II were obtained from individuals who had been operated upon less than six months prior to the check-up examination. At the time we made this study there were 69 who had only been six to seven months. Thirty-nine per cent of these were helped. But in a group 9 to 15 months

postoperative, 46 per cent showed improvement and for the 18 to 30 months group, or 42 per cent. That the improvement persists is shown in the group who had gone 33 to 60 months, where 52 per cent still showed a maintained reduction. Our total group of patients, of all ages, shows a maintained worthwhile drop in blood pressure in 46 per cent.

TABLE II

BLOOD PRESSURE REDUCTION IN CASES GROUPED BY LENGTH OF POSTOPERATIVE PERIOD

Group by Months	Number of Cases	Number Reduced	Percentage Improved
6 mos.....	69	27	39.2%
9–15 mos.....	107	50	46.7%
18–30 mos.....	98	42	42.8%
33–60 mos.....	48	25	52.0%

We figured not only blood pressure improvement, but also improvement in all the other factors which seem to be influenced either by the high blood pressure or are associated with it. Forty-four per cent have shown a maintained improvement in their water concentration, and the same in urea clearance. Symptomatic improvement was noted by Doctor Davis in a good many of his patients with sulphocyanate. We had 87 per cent of our patients practically free of their symptoms of headaches, dizziness, etc. I think the most significant change, certainly from the economic standpoint, is improvement in incapacitation. Eighty-four per cent have shown worth while improvement, and 58 per cent have had complete recovery. This 58 per cent represents a group who were completely incapacitated prior to operation and now are back at their original jobs working as hard as ever (Table III).

TABLE III

PERCENTAGE OF CASES SHOWING IMPROVEMENT FROM SIX MONTHS TO FIVE YEARS AFTER OPERATION

Blood pressure	46%
Water concentration	44%
Urea clearance	44%
Symptomatic	87%
Incapacitation	84%
(Complete recovery of incapacitation)	58%

Now, perhaps, we can add to this group of 58 per cent another group restored to a useful life by sulphocyanate therapy after splanchnicectomy. We have only employed potassium sulphocyanate in three individuals at the University Hospital, after splanchnicectomy. I think it is advisable to wait for some time before administering sulphocyanate, because we have had a good many patients whose blood pressure was not improved in the first month or so, but who later showed a gradual improvement over several months.

We do not figure surgical results until at least a six months' postoperative period has elapsed. I think we should wait until after that length of time. If no improvement is noted after the blood vessels have had a chance to recover, then sulphocyanate should be tried. While we have only tried sulphocyanate therapy in three postoperative cases at our hospital, I have frequently suggested to the physicians who have referred cases which did not respond to splenchnicectomy that they follow the sulphocyanate treatment as outlined by

Doctor Barker in the Journal of the American Medical Association for March 7, 1936.

Of the three that we have had in our clinic, two did not respond to sulphocyanate therapy following splanchnicectomy. The third did. That patient was kept on sulphocyanate for some time, then the sulphocyanate was stopped, the blood pressure immediately rose and the symptoms returned. Sulphocyanate was again administered but without improvement.

DR. ALFRED BLALOCK (Nashville, Tenn.): I can throw no light on the explanation for these important findings of Doctors Davis and Barker. From an academic viewpoint, it seems to be of particular importance that patients with hypertension and dogs with hypertension due to renal ischemia frequently respond in the same way to this method of therapy. As the experimental evidence increases, it becomes more certain that there must be a great many patients with unexplained hypertension in which renal ischemia is at least a partial factor.

As you may know, if one produces ischemia of one kidney by the use of the Goldblatt clamp, the blood pressure will rise for two or three weeks, and then it is apt to return to the control level. If, after this blood pressure returns to the control level, one takes out the opposite normal nonischemic kidney, usually the blood pressure will rise again, which indicates that the nonischemic kidney may be a factor in determining the response to ischemia. This has suggested to a number of workers that the normal kidney may contain or be able to make an antipressor substance which plays a rôle in maintaining the normal blood pressure. Please bear that in mind for a moment, as I will return to it.

In a series of experiments, Doctors Levy, Cressman and I determined the effects of intestinal ischemia on the blood pressure. By producing gradual occlusion in multiple-stage operations, we could completely occlude the celiac axis, the superior mesenteric artery and the inferior mesenteric artery. A temporary rise in blood pressure occurred with these procedures, but the pressure returned almost but not quite to the control level.

If, in an animal with intestinal ischemia, one places a clamp upon the artery to one kidney leaving the other kidney undisturbed, in most instances one will get a sustained rise in blood pressure, which in some experiments has persisted now up to 20 months.

As stated, unilateral renal ischemia alone usually results in only a temporary rise in pressure. We have demonstrated the effect of unilateral renal ischemia in an animal in which complete constriction of the main vessels to the intestinal tract had been produced previously. There was a slight rise in blood pressure associated with intestinal ischemia. We then produced constriction of the artery to one kidney, and during a 15-month period this animal was followed, the mean blood pressure remained at the level of approximately 200 Mm. Hg. Splanchnicectomy had no effect whatever upon the pressure. I might say that this animal became pregnant several months ago, delivered four normal puppies; eclampsia did not occur.

The only point I am trying to make is that it would seem that these experiments throw doubt on the possibility of obtaining from a normal kidney something which will reduce the blood pressure in hypertension.

DR. WILLIAM JASON MIXTER (Boston): It seems to me that this paper of Doctor Davis' brings up one very interesting point in regard to this whole subject of hypertension. I think we all have to admit that the subject of hypertension is very much mixed up at the present time, the results are not comparable in different clinics, and why we have these different results in

various clinics, we do not know. If we could get closer together in our criteria for our surgical procedures, we might be more in agreement in our results.

I think that what Doctor Davis has done in splitting off a small group of cases and trying to find out what happens with that one individual group, is a very valuable thing, and the more that we can standardize even our own individual criteria and follow them in small groups of cases, the sooner this problem will be decided.

Dr. George Crile (Cleveland): I have had the opportunity in three instances of operating for essential hypertension with a slightly different objective. Seven years ago, I operated upon two cases in which the disease was in a very early stage; the diagnosis being based principally upon the eyegrounds. Within the last week, I have had the opportunity of examining one of these older cases. The patient went through the Clinic and no one who examined him could find any sign of essential hypertension. I mention this because when an early stage of essential hypertension has been established in such cases, such as have been referred to this morning, the fact that surgery can accomplish something worth while for them puts us in a position where we were long ago when considering operation for cancer of the breast for example, or for appendicitis. It was quite a long time before public opinion among the internists agreed that surgery could do something worth while for the patient with early carcinoma. When that fact was established we had the opportunity for operating early. It would seem, from this meager clinical experience, that patients operated upon in the early stage of hypertension that this early operation will be as effective as an early operation is in cases of cancer or in the treatment of appendicitis.

Dr. Loyal Davis (Chicago): I simply wish to emphasize that the adequate treatment of essential hypertension by cyanates requires the establishment of an accurate blood cyanate level for the particular individual under treatment. This level varies with each individual. In this way, only, can the patient be safeguarded against the symptoms of toxemia which often result from the injudicious employment of cyanates.

Exactly where the cyanates act and how they act is unknown. This remains a problem for physiologic experimentation, and is one in which we are engaged at present.

The excellent experiments of Doctor Blalock and others are important steps, which eventually may lead to the explanation of the entire problem of hypertension and the effect of any procedure which may be carried out. I can only say about Doctor Peet's cases, that I would feel that the cases of many of the patients operated upon who have responded so well to splanchnicectomy alone would correspond to the cases of those patients in our group who have reacted definitely and sensitively to small doses of cyanates.

THE RÔLE OF THE PITUITARY GLAND IN WATER BALANCE*†

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THE PROBLEM of determining the rôle played by the pituitary gland in water balance is not a new one to members of the American Surgical Association. Cushing[1] and his associates were the first to investigate the subject from both the experimental and the clinical standpoints. In their report of 1909, they held the view that the loss of the glandular division of the hypophysis was responsible for the development of diabetes insipidus. This idea was soon abandoned, and, in 1913, they[2] postulated that a loss of the posterior lobe was responsible. They found it more difficult to correlate this interpretation with the erroneous, but widely accepted, conclusions of Schafer and Herring[3] (1905), that the extract of the posterior lobe of the pituitary normally exercised a diuretic function. Von der Velden[4] (1913) and Farini[5] (1913) soon reported, however, their successful treatment of diabetes insipidus with pituitrin. Numerous clinical and pathologic reports followed, which, on analysis, indicated that the significant organic changes associated with diabetes insipidus were always intracranial, especially those in the region of the hypophysis and hypothalamus. Aschner[6] (1912) reported that in dogs the loss of the pituitary gland did not result in diabetes insipidus. From this and an analysis of clinical cases, von Hann[7] (1918) postulated that diabetes insipidus was due to a loss of the posterior lobe but that some anterior lobe must remain present.

Investigators in the field became divided into two groups—the hypothalamists, who held that the hypothalamus was primarily involved in diabetes insipidus, and the hypophysists, who held that the loss of the pituitary gland itself was responsible. Among the former were Camus and Roussy[8] (1913 to 1925), Bailey and Bremer[9] (1921), Curtis[10] (1924), Reichert and Danby[11] (1936), and Mahoney and Sheehan[12] (1936). Keller and his associates[13] (1936 and subsequent papers) were first hypothalamists, but in his latest report Keller[14] (1938) states that diabetes insipidus is due to a lack of antidiuretic secreting tissue normally found in the posterior lobe, stalk, and hypothalamus. He finds that a submaximal permanent diabetes insipidus may exist without

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anterior lobe tissue, but that anterior lobe tissue is essential for a maximum diabetes insipidus. Richter[15] (1927 to 1936), Fisher, Ingram, and Ranson[16] (1935 to 1939), and White and Heinbecker[17] (1937 to 1939) regard the essential lesion to be in the neural division of the hypophysis in which term is included the median eminence, infundibular stem, and the pars nervosa. This division of the hypophysis is under the nervous control of the hypothalamico-hypophyseal system. Degeneration of this system leads to degeneration of the pituicytes of the neural hypophysis with a loss of their secreting power.

Neural Hypophysis and the Hypothalamico-Hypophyseal System—In 1915 and in subsequent papers, Tilney[18] showed definitely that in mammals the neural hypophysis is composed of three divisions—the median eminence, the infundibular stem, and the pars nervosa—while the glandular division consists of the pars tuberalis, pars intermedia, and the pars anterior. Cajal[19] (1894), working on the rat, was the first to demonstrate a neural connection between the hypothalamus and the neural hypophysis. Kary[20] (1924) revived interest in the subject by redescribing the hypothalamico-hypophyseal tracts and by showing that the supra-optic nucleus may be degenerated in diabetes insipidus. Trendelenburg and Sato[21] (1928) advanced evidence that an antidiuretic substance could be extracted from tissue of the hypothalamus (medium eminence, probably) in the absence of the hypophysis. Maiman[22] (1930) demonstrated experimentally degeneration of the supra-optic nucleus following destruction of the tract. Broers[23] (1932) reported the occurrence of diabetes insipidus in dogs after bilateral destruction of the supra-optic nuclei or a lesion of the stalk producing atrophy of the former. Beginning in 1935, Fisher, Ingram, and Ranson[16] have published a series of papers in which they showed that permanent polyuria followed the production of lesions limited to the hypothalamus provided that the lesion interrupted the hypothalamico-hypophyseal tracts. Additional evidence pointing to the anatomic and functional similarity of the median eminence, the infundibular stem, and the pars nervosa has been provided by Wislocki and King[24] (1936), who showed that on the injection of vital dyes phagocytosis occurred in these three regions and in no other parts of the hypothalamus. The failure of investigators to take cognizance of the facts above described has been responsible for much of the confusion in determining the anatomic basis for diabetes insipidus.

Anatomic Basis for Diabetes Insipidus.—To determine the anatomic basis for diabetes insipidus, we have carried out various operative procedures on the hypophysis, the hypothalamus or on both of these structures of more than 100 dogs. The approach was either by the temporal or the buccal route. The lesions consisted of hypothalamic punctures so placed as to interrupt the hypothalamico-hypophyseal tracts (Fig. 1A); high stalk sections (Fig. 1B) with or without removal of the glandular hypophysis; low stalk sections (Fig. 1C) with or without removal of the grandular hypophysis; total destruction and removal of the neural hypophysis (Fig. 1D) with removal of the glandular hypophysis. In some animals the glandular hypophysis was removed two to four months after successful hypothalamic puncture. The animals were kept

in metabolism cages for two to ten months on a constant diet of Purina dog chow and meat; milk was sometimes given for a few days postoperatively. Daily urine collections were made; the fluid intake and urine specific gravity were also followed at times. After completion of the period of observation the animals were sacrificed and the brains fixed *in situ*. The hypothalamus together with the skull in the region of the sella turcica was examined microscopically in serially cut 20 micron sections. In this way the extent of the lesion, the condition of the hypothalamic nuclei and of the hypophysis were accurately determined.

In this presentation no attempt will be made to analyze the data secured. The results will be indicated by a brief statement of the findings in some typical experiments.

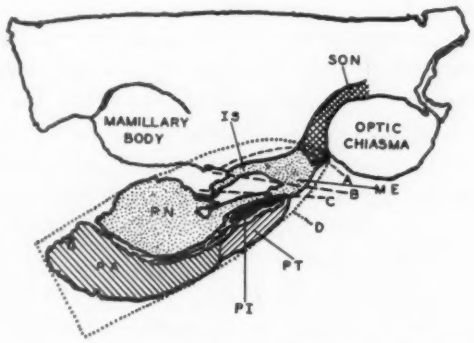

FIG. 1.—Drawing of sagittal section of dog's hypothalamico and hypophyseal regions indicating the extent of operations designated A, B, C and D in the text. SON, supra-optic nuclei; ME, medium eminence; IS, infundibular stem; PT, pars tuberalis; PI, pars intermedia; PN, pars nervosa; PA, pars anterior.

Following hypothalamic puncture resulting in successful interruption of the hypothalamico-hypophyseal tracts (lesion A, Fig. 1), there results a temporary high polyuria (8 to 15 times normal) which in three to eight days is followed by a return to normal or near normal water exchange. This in turn is followed in a few days by a permanent high polyuria (8 to 15 times normal). Microscopically, there is found a disappearance of the cells of the supra-optic and filiform nuclei. There are atrophy and hypercellularity of the neural division of the hypophysis; a large portion of the glandular division is left in a normal state.

When a hypothalamic puncture (lesion A, Fig. 1) is made and the glandular division of the hypophysis together with the infundibular stem and pars nervosa are removed at the same operation, there follows an immediate polyuria (five to ten times normal) lasting three to eight days which is followed by a period of normal or near normal fluid exchange lasting eight to 20 days. Then there follows a rather sudden increase to a permanently elevated fluid exchange four to eight times the normal. When the median eminence is also removed in this type of operative procedure (lesion D, Fig. 1) the normal interphase is or tends to be eliminated. Microscopically, the cells of the supra-optic and filiform nuclei are found absent, the median eminence is atrophied or absent (if removed at operation) and there is no trace of pars nervosa or glandular hypophysis.

If, in animals in which a successful interruption of the hypothalamic tract (lesion A, Fig. 1) has resulted in a permanent high polyuria, a nearly complete removal of the glandular division of the hypophysis is carried out two to four months after the original puncture, *there results no diminution in poly-*

uria. Microscopic sections of the hypothalamus and skull of nine such animals have shown that we have not succeeded in removing entirely all of the anterior lobe. In each instance, 3 to 5 per cent of the pars anterior has been found embedded in the scar tissue at the posterior end of the sella. In seven instances, it was felt that the microscopic appearance of the cells remaining warranted the belief that they were capable of functioning. It was not possible to exclude the possibility in the two instances where the cells did not have a normal appearance. The amount of anterior lobe present was not enough to prevent atrophy of the gonads and a narrowing of the adrenal cortex.

In animals in which a high stalk section (lesion B, Fig. 1) was made there developed a moderate temporary polyuria one to three times the normal of one to three days' duration, followed by a return to permanently normal water exchange level. Microscopically, such brains showed an estimated loss of about 50 per cent of the cells of the supra-optic and filiform nuclei. The pars nervosa was atrophied and hypercellular; the glandular division of the hypophysis and the median eminence were essentially unchanged.

Animals in which a low stalk section (lesion C, Fig. 1) was made with or without removal of the pars nervosa and glandular division of the hypophysis, showed no increase in fluid exchange or a very temporary one of one to three days' duration. Microscopically, the brain showed a 30 to 50 per cent atrophy of the supra-optic and filiform nuclei, a normal median eminence, an absence of the remainder of the hypophysis in those instances where its removal was attempted. When not removed the pars nervosa became atrophied; the anterior lobe remained normal. It seems clear that the anterior lobe receives an adequate blood supply from below or through newly established channels after its complete separation from the brain and even that small fragments of the stalk left behind in the sella in an attempted complete removal may survive.

Analysis of the above results permits the statement that a maximal polyuria never follows unless there is a complete loss of the supra-optic and filiform nuclei.

The Rôle of the Anterior Lobe in Water Balance.—Our experimental results indicate that the permanent phase of diabetes insipidus resulting from removal of the neural division of the hypophysis is less than the maximal possible when the glandular division of the hypophysis is also removed at the same operation. When the glandular division is removed two to four months after maximal diabetes insipidus (8 to 15 times normal) has been established by hypothalamic puncture its loss *seems* to have no consequences. It is not possible to state definitely that the small residual fragment of anterior lobe (3 to 5 per cent) found in all our dogs of this class is of no consequence, but our present evidence speaks in favor of this view. Experimental proof is being obtained to settle the point. It is felt that under normal conditions the anterior lobe plays a diuretic rôle. Elsewhere in this paper, it will be shown that it acts synergystically with the secretion of the thyroid gland in stimulat-

ing water excretion. It is possible to remove or destroy part of the neurohypophysis in such a way that the presence or absence of polyuria depends upon the presence or absence of anterior lobe. These findings indicate a diuretic effect of the anterior lobe; they are not incompatible with our present belief that the anterior lobe is not essential to the maintenance of a maximal and permanent polyuria previously established by a *complete destruction of all elements of the neurohypophysis.* While, as stated above, the evidence for this belief is not at present complete, we can state positively that maintenance of a maximal and complete polyuria is not impaired by removal of 95 to 97 per cent of the anterior lobe.

The Effect of Thyroid on Urine Output.—When 0.1 Gm. of desiccated thyroid per kilo is fed to normal dogs the increase in urine output usually ranges from zero to 50 per cent. Thyroidectomy in normal dogs produces slight if any permanent decrease in urine output. When thyroidectomized dogs are given the above dose of desiccated thyroid their urine output is little if any increased.

It has been held by Barnes, Regan, and Bueno[25] (1933) and others that the action of pituitary anterior lobe extract is mainly through stimulating the thyroid gland. To test this hypothesis experiments were carried out on dogs, some of which had been modified by various operative procedures, with the following results:

It was found that the daily administration of 1.7 to 2 cc. of anterior lobe extract (0.25 gr. fresh tissue per cc.) per kilo of body weight usually increases the urine output of normal dogs two- to fivefold; the increase appears within the 24 hours and lasts three to six days. Similar results were obtained in the hypophysectomized dogs recovered from the transient polyuria.

The daily administration for six to eight days of 0.1 gr. of desiccated thyroid per kilo produces no significant change in the daily urine output of either hypophysectomized or hypothysectomized-thyroidectomized dogs. The daily addition for two days of 2 cc. of anterior lobe acid extract per kilogram during a period of thyroid administration, beginning after six to eight days of thyroid, produces in hypophysectomized dogs an increase in daily urine output about the same as the anterior lobe alone. Daily administration for two days of 2 cc of anterior lobe extract per kilo does not produce any increase in urine output in the hypophysectomized-thyroidectomized dog within the first few weeks after thyroidectomy but may produce an increase, although smaller than in the normal or thyroid-fed animal, if given two months or later after thyroidectomy. The daily administration for two days of 2 cc. of anterior lobe extract per kilo to the hypophysectomized-throidectomized dog during a period of thyroid administration (0.1 gr. per kilo daily) shows results essentially the same as those seen in hypophysectomized dogs before thyroidectomy (Chart 1).

Effect of Thyroidectomy in Experimental Diabetes Insipidus.—The effect of thyroidectomy on the transient phase of diabetes insipidus is to abolish it within 24 to 48 hours. Such an effect is, however, not obtained when thy-

roidectomy is carried out during the permanent phase of polyuria. In the latter case the effect apparently depends upon the length of time which has elapsed after destruction of the neural division of the hypophysis. The earlier in the permanent phase thyroidectomy is carried out, the greater is its antidiuretic effect. After four to six months it was found in the two dogs so investigated that no effect at all on urine output resulted from thyroidectomy. It can be stated on the basis of our observations and those of Ranson and his collaborators[26] (1938) that usually no more than a 50 per cent decrease in polyuria, and often less, can be expected from thyroidectomy when a state of diabetes insipidus exists in dogs and cats.

Effect of Thyroidectomy in Human Diabetes Insipidus.—A similar finding to that observed in experimental diabetes insipidus resulted in one human case: A male, colored, age 55, with central nervous system syphilis and diabetes insipidus of three years' duration, which had not yielded to antiluetic therapy, was completely thyroidectomized in August, 1936. The pre- and postoperative findings are shown in Chart 2. After thyroidectomy, there was a 25 to 30 per cent decrease in urine output on a normal diet with unrestricted salt intake. The patient insisted that his thirst and polyuria were much less disturbing than before operation. On a low-salt diet the average 24-hour urine output after thyroidectomy was essentially the same as on the same diet before thyroidectomy. The urine volume was increased less by salt administration and diminished more by pitressin after operation than before.

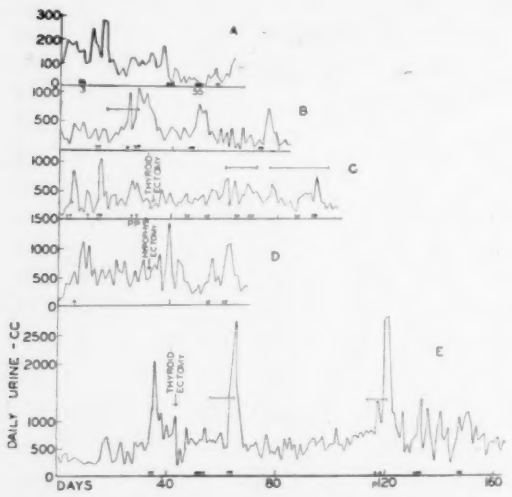

CHART 1.—=desiccated thyroid, 0.1 gm. per kilo. ▲=anterior lobe extract, 1.7 to 2 cc. per ilo. P=Phyone. Where more than two cubic centimeters per kilo of extract were given, the figure under the arrow desgnates the dose in cubic centimeters per kilo. A=normal female monkey; B=male dog, hypophysectomized 15 days before beginning of chart; C=male dog, hypophysectomized three months before beginning of chart, thyroidectomized as indicated on chart; D=male dog, hypophysectomized as indicated on chart; E=male dog, hypophysectomized 18 days before beginning of chart, thyroidectomized as indcated on chart.

The findings indicate there exists in beef anterior lobe extracts a diuretic principle which cannot act in the absence of thyroid in the acutely thyroidectomized animal but does have a moderate effect in the chronically thyroidectomized animal. That this diuretic principle is not merely the thyrotopic hormone is indicated by the finding that with a constant intake of thyroid by mouth, insufficient in itself to produce diuresis, the thyroidectomized dog shows a diuretic response to anterior lobe administration which is not effective without the thyroid. The effect of the thyroid appears to be that of a sensitizing agent for the diuretic principle of the anterior lobe.

Experiments to determine whether the ability of the thyroid to render effective the diuretic action of anterior lobe is specific or is due to its effect on general metabolism have been reported by White, Heinbecker, and Robertson[27] (1938) (Chart 3). Dogs were rendered moderately diabetes insipidus by incomplete hypothalamic puncture; this polyuria was reduced but not abolished by subsequent thyroidectomy. When 0.1 gr. of desiccated thyroid is now given to such animals the polyuria is restored essentially to the pre-

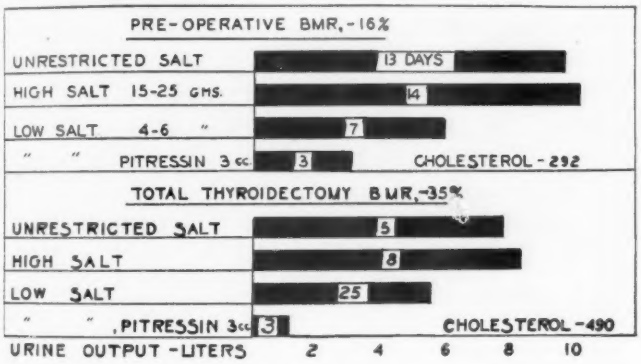

CHART 2.—*Urine Output Before and After Total Thyroidectomy in Human Case:* Each rectangle represents the average 24-hour urine flow for the number of days enclosed within it. Fluid intake was unrestricted throughout; the values are not recorded because they closely paralleled the urine volumes in every period.

thyroidectomy level. However, a daily dosage of 3 mg. of dinitrocresol per kilo (which produced the same elevation of basal metabolic rate as the above thyroid dosage) has no diuretic effect. This indicates that the action of thyroid, which is synergystic with the diuretic action of anterior lobe, is probably not due to the former's effect in elevating the basal metabolic rate.

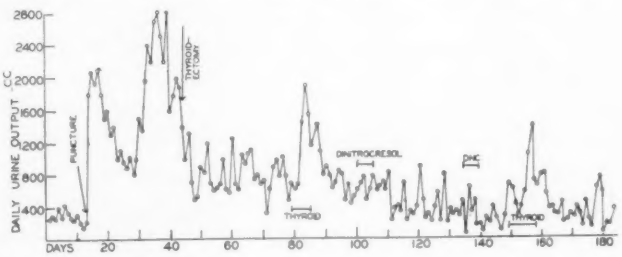

CHART 3.—Effect of thyroidectomy and of thyroid and dinitrocresol administration on daily urine output of polyuric dog.

Primacy of Polyuria.—That the polyuria and not the polydypsia is primary, has been shown by Richter[15] (1927), Fisher, Ingram and Ranson[26] (1938) and by others. We have confirmed the observations of these investigators in this matter.

Site of Action of Pitressin.—It has been held by some, that the site of action of pitressin is in the kidney and by others in the body tissues generally or in some hypothetic water center of the hypothalamus. It is considered by us

that pitressin acts on the kidney for the following reasons: First, Starling and Verney[28] (1926) have shown that pitressin administered in doses which do not affect blood pressure acts as an antidiuretic on the isolated perfused kidney. Second, it has been shown repeatedly that pitressin does not alter the water or salt content of the blood plasma in normal or diabetes insipidus animals or the colloidal osmotic pressure in normal animals. Third, if pitressin is given to an individual after a large drink of water, diuresis is prevented even when the amount of blood dilution is such as would cause a diuresis had no pitressin been administered.

Transient and Permanent Phases of Diabetes Insipidus and Normal Interphase.—Following any of the above operative procedures, there may appear

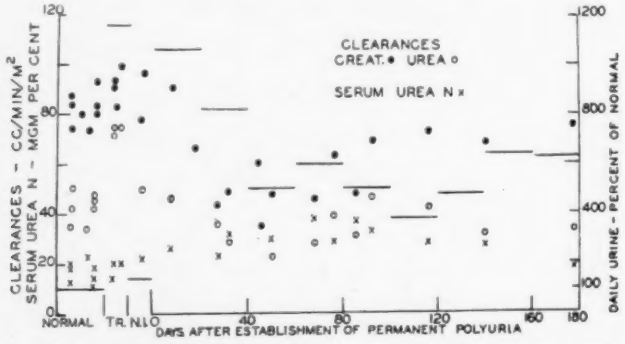

CHART 4.—Daily urine output in averages of 20-day periods; creatinine and urea clearances and serum urea N. before and after establishment of polyuria. This chart shows the findings on five diabetes insipidus dogs. Urine outputs are expressed as percentages of the normal, averaged for 20-day periods in all five dogs, and shown as the horizontal lines. Left section of figure, labeled Normal, shows urine output (100 per cent) and clearances during the preoperative observation periods of 24 to 53 days with the various dogs. Transitory phase of polyuria: Tr. and normal interphase, N.I. Horizontal axis expresses time quantitatively after zero day.

a transient increase in fluid exchange varying from two to ten times the normal. It makes its appearance from several hours to 24 hours after operation. It lasts from one to 10 or 12 days and is then followed by a return to a normal or nearly normal level of fluid exchange (normal interphase). In those instances where there has been a severance of the neural division of the hypophysis from its neural connections with the supra-optic and filiform nuclei of the hypothalamus, this normal interphase is followed in five to 20 days by a rather sudden return to an increased fluid exchange essentially as great as occurred during the transient phase. This is called the permanent phase of diabetes insipidus. The transient phase is considered to be due to a functional elimination of the pituicytes by injury. On recovery a normal fluid exchange results because their secretion is reestablished. When a normal interphase precedes a permanent polyuria, its duration is considered to coincide with the time necessary for denervated pituicytes to lose their secretory functions.

Creatinine and Urea Clearances in Diabetes Insipidus and Hypophysectomized Dogs.—Diabetes Insipidus: In general, creatinine clearance is unchanged during the transitory polyuria. Urea clearance is somewhat elevated

but this is probably because of the greater urine flow. Creatinine and urea clearances during the normal interphase between the transitory and permanent polyurias are normal. These clearances remain normal for one to two weeks after the onset of the permanent polyuria and then both gradually fall, creatinine reaching a level approximately half the normal by four to six weeks after operation. Urea clearances fall less than creatinine and may not fall at all even with 50 per cent fall in creatinine; this may result in an unusually high rate of urea to creatinine clearance values. This situation is complicated by the fact that, on the average, the urine flows during the clearance periods of the permanent polyuria were somewhat higher than during normalcy or latent period. This would work in the direction of raising urea clearances. A slight fall or no change under our conditions might have been a more definite fall if urine flow rates could have been kept constant during all clearance periods. The values have returned not quite but almost to normal after 175 days of permanent polyuria. The above statements are based on 20 creatinine and 22 urea clearance values made on five dogs preoperatively and at various times after production of a lesion which resulted in permanent diabetes insipidus, where each clearance value is the average of three consecutive 30-minute clearance periods (Chart 4).

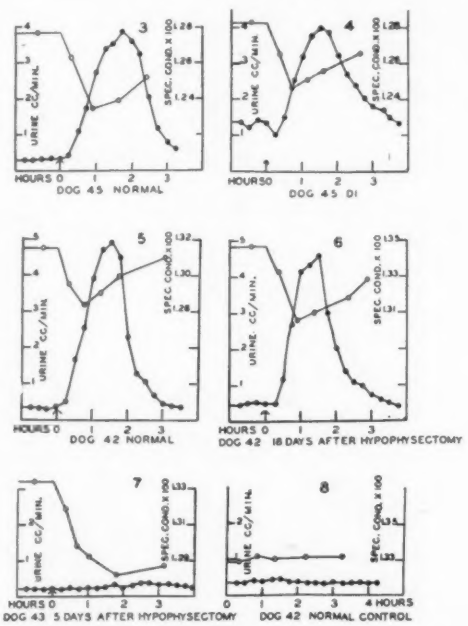

CHART 5.—Serum electrolyte dilution and urine output responses of dogs to 3 per cent body weight of water; serum specific conductivity in reciprocal ohms; urine output in cubic centimeters per minute. Three per cent body weight of water by stomach tube at zero hour except in Figure 8, which shows a control, *i.e.*, normal dog with no water administration.

Hypophysectomy.—Creatinine and urea clearances fall after hypophysectomy with polyuria and are returning toward normal at the end of a few weeks (Chart 4).

Response of Dogs with Diabetes Insipidus to Water Administration.—The response of five dogs with diabetes insipidus to the administration of 3 per cent of body weight of water given by stomach tube has been compared with that of 13 normal dogs and three hypophysectomized dogs without polyuria. Urine samples were obtained every 15 minutes by catheterization for four or more periods, the water was then administered by stomach tube and urine samples again collected every 15 minutes for three to four hours or until the urine flow reached a normal level. Blood salt dilution was determined by measuring the serum specific conductivity in terms of ohmic resistance at in-

tervals before and after the water administration; in some cases serum viscosity was also followed as an index of protein content. Typical response curves are shown in Chart 5.

The results indicate that the diuretic responses of normal dogs, hypophysectomized dogs without polyuria, and diabetes insipidus dogs are similar. It is of interest to note here that, in contrast, the chronic human diabetes insipidus patient shows little or no diuretic response to 3 per cent body weight of water by mouth. For reasons not yet understood, dogs during the first 10 days after hypophysectomy also show little or no diuretic response to such a dose of water. The results do not support the view of Verney and his collaborators[29] (1933) that the lag in water output behind water load represents the time for preformed pitressin to disappear. In our diabetes insipidus dogs there was presumably little or no preformed pitressin present and still the lag was similar to that found for the normal dog.

TABLE I

AVERAGE CONCENTRATION OF URINE AFTER 24 HOURS OF WATER DEPRIVATION

	Specific Gravity	Creatinine Mg. Per Cent	Urea N. Mg. Per Cent	NaCl. Mg. Per Cent
Normal preoperative	1.068	190	4270	1100
Postoperative diabetes insipidus	1.035	145	1670	860
Normal preoperative	1.064	220	4100	1050
Postoperative hypophysectomized	1.040	160	2100	1020

Effect of Water Deprivation in Dogs with Diabetes Insipidus.—The effect of depriving diabetes insipidus and hypophysectomized dogs without polyuria of water for 24 hours is shown in Table I. The figures represent the averages obtained on three dogs of each type before and after operation. Diabetes insipidus dogs can concentrate to a specific gravity of about 1.030, but normal dogs can concentrate up to a specific gravity of 1.065. Neither the normal nor the hypophysectomized dogs show any greater concentration after 48 hours than after 24 hours. The diabetes insipidus animal can hardly tolerate more than 24 hours of water deprivation. After that time, gradually developing weakness becomes marked and unconsciousness supervenes. Restorative measures, in the form of intravenous normal saline, are effective if given early after the development of such symptoms.

SUMMARY AND CONCLUSIONS

Experimental evidence is presented to indicate that diabetes insipidus results only after functional or anatomic removal of all the neural hypophysis, *i.e.*, pars nervosa, stalk, and median eminence.

The anterior lobe, while not essential for the existence of the permanent state of diabetes insipidus, normally probably plays a diuretic rôle.

The diuretic effect of the anterior lobe is not exerted solely through its

thyrotropic action nor in the maintenance of a normal basal metabolic rate. The anterior lobe and the thyroid appear to be synergistic.

Total thyroidectomy in human diabetes insipidus may result in a diminution of urine output of approximately 30 per cent. On the basis of experimental evidence, it would be expected to vary from zero to 50 per cent.

Creatinine clearance is unchanged during the transitory phase of experimental diabetes insipidus. Urea clearance is somewhat elevated, probably because of increased urine flow. During the normal interphase period both clearances are normal. Creatinine clearance reaches a level approximately half the normal by two to four weeks after the onset of permanent polyuria. It remains down for a variable time and then gradually returns toward normal, which may be almost reached after six months of permanent polyuria. Urea clearance falls less than does creatinine clearance during the phase of permanent polyuria and may not fall at all. Serum urea rises as clearances fall early in permanent polyuria but shows a later return toward normal.

Hypophysectomized or diabetes insipidus dogs, in which exists a more or less complete chronic deficit of pitressin, show no significant alteration from the normal in the time relations of their blood dilution and urine output responses to ingestion of 3 per cent body weight of water. This is interpreted as indicating that the lag of maximum rate of water output behind maximum blood dilution after water drinking in the normal is not due to the time required for preformed pitressin to disappear. Within the first week or 10 days after hypophysectomy there may be only a slight and delayed diuretic response to water by mouth.

After 24 hours of water deprivation, the ability of hypophysectomized dogs without polyuria and of diabetes insipidus dogs to concentrate urine is impaired about 50 per cent with respect to urea, 25 per cent with respect to creatinine, and unchanged with respect to chlorides. The ability of hypophysectomized dogs without polyuria to tolerate water deprivation is as great as that of the normal but that of diabetes insipidus dogs is greatly decreased.

The authors wish to acknowledge permission to reproduce Charts 2 and 3 from Volumes 36 and 38 of the Journal of the Society of Experimental Biology in Medicine; and Charts 1, 4 and 5 from Volumes 118 and 123 of the American Journal of Physiology.

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Discussion.—Dr. Loyal Davis (Chicago): The hypothalamus and the hypophysis are very closely associated anatomically and functionally. In the past, it has been very difficult, experimentally, to produce a lesion of the hypophysis without producing injury to a hypothalamus. Consequently, in the literature there has grown up a group of "hypothalamists" and a group of "hypophysists," each of whom believes that the results of their experimental work have been due to a lesion of the hypothalamus or, on the other hand, to removal of the hypophysis.

Diabetes insipidus constituted a very perplexing problem, to which many investigators have paid attention. Clinically this has been of great interest to neurologic surgeons because of the association of diabetes insipidus with tumors apparently confined to the hypophysis.

Recent refinements in operative technic and experimental surgery have made it possible to remove a portion of the hypophysis or all of that gland without damage to the hypothalamus, as Doctor Heinbecker has shown in his work which has been controlled by serial sections of the midbrain. From another standpoint, Doctor Heinbecker's results may be caused as due to a lesion of the hypophysis alone because they are duplicated by results obtained by Doctor Ranson as the result of producing an electrolytic lesion with the Horsley-Clarke stereotactic instrument.

It seems to me that the whole problem which Doctor Heinbecker presents so well, resolves itself to a statement that diuretic processes are entirely under control of the anterior lobe of the hypophysis. This is quite distinct from the old view that these processes were under the control of the posterior lobe. Therefore, polyuria may be thought of as resulting from an uncompensated activity of the anterior lobe or a disease and, therefore, the result of an imbalance between the anterior and posterior lobes of the hypophysis. There is

still some difference of opinion as to the exact manner in which the anterior lobe exercises this diuretic influence.

Doctor Ranson and his associates, working upon thyroidectomized cats, have obtained results similar to those of Doctor Heinbecker. Their work is, however, contrary to that of Mahoney and Sheehan who found that diabetes insipidus, produced in dogs by a lesion of the stalk of the pituitary gland, could be made to disappear after a thyroidectomy. As both Ranson and Heinbecker point out, there is a strong probability that the polyuria of Mahoney's and Sheehan's dogs was not a permanent one.

Finally, to emphasize the importance of the small area in the midbrain known as the hypothalamus, I need only to remind you that just a few millimeters away from the point where Doctor Heinbecker has performed his operations and where Doctor Ranson has made his lesions, are the periventricular nuclei. At the Toronto meeting of this Association some years ago we showed that a lesion of those nuclei prevented the diabetes mellitus which could be reproduced in animals by the removal of the pancreas though the hypophysis was untouched and remained intact.

THE CONTROL OF WATER AND ELECTROLYTE BALANCE IN SURGICAL PATIENTS*

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The management of water and electrolyte balance is one of the most important aspects of modern surgery. Although this subject began to receive attention in the treatment of cholera a century ago,[1] the general problem has been elucidated only within recent years.[2] As a result of fundamental work in biochemistry and physiology a new point of view has developed in the treatment of intestinal obstruction, severe burns and other conditions showing a disturbance of electrolyte and water balance. Practical methods for the management of these conditions in surgical patients have been proposed by several authors,[3, 4, 5, 6, 7] the value of which methods is attested by a literature too voluminous for citation here.

Because of certain limitations in methods proposed to date, further studies were undertaken. The present report describes a routine developed at the Pennsylvania Hospital for the control of electrolyte and water balance in patients undergoing serious surgical procedures. Emphasis is placed on simultaneous determination of hematocrit values, plasma protein and total base as giving a fairly accurate picture of the state of hydration and electrolyte balance.

Physiologic Considerations.—From the physiologic standpoint three factors must be considered in the care of patients with a disturbance of the water and electrolyte balance: (1) The degree of hydration; (2) the electrolyte balance; and (3) the state of nutrition. These factors will be reviewed briefly.

The water of the body may be divided into three fractions: Intracellular; interstitial; and intravascular. These fractions and the shift of water between them are graphically illustrated by Gamble.[8] The interstitial and the intravascular fractions together make up the extracellular water. The interstitial fraction is normally about three times as large as the intravascular, and is a great reservoir whose volume fluctuates widely in varying degrees of hydration while that of the intravascular fraction (plasma volume) is maintained at a constant level. This extensive reservoir of interstitial water, or "swamp" as Cannon[9] calls it, may be relatively "wet" or "dry," but it maintains a steady volume in the vascular tree or "river."

The essential problem in estimating the degree of hydration is the determi-

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nation of the volume of water in the "swamp" and the "river," the extracellular volume. At the present time, methods for the direct measurement of the extracellular water volume[10] have not been adopted as a routine clinical procedure. Direct weights showing serial changes are suggestive, but these are difficult to obtain in clinics where accurate stretcher scales are not available for bedridden patients, and frequently patients are received in a dehydrated state where the normal weight is not known. Practically, aside from clinical signs, the extracellular water volume can be approximated only by considering indirect evidence obtained from its intravascular portion, the plasma.

Plasma volume is maintained at the expense of interstitial water during extracellular water loss, up to a certain point.[11] Beyond this point, the plasma volume diminishes with resulting hemoconcentration. Hemoconcentration or diminished plasma volume, therefore, indicates a serious depletion of the extracellular reservoir,[12] but does not measure that depletion quantitatively.

One of the simplest clues to plasma volume is the hematocrit which measures the relative proportion of plasma to erythrocytes.* In the absence of progressive changes in the total number of erythrocytes, such as with hemorrhage or with transfusion, serial hematocrit values reflect changes in plasma volume.[13] Although shifts in *p*H cause some variation in the volume of the erythrocyte and thereby affect the hematocrit value,[14] such changes are negligible in comparison with those resulting from alterations of plasma volume. Likewise, changes in plasma protein concentration, where there is no protein addition or loss, may reflect changes in plasma volume. These determinations, therefore, may be used to advantage in detecting more serious degrees of dehydration.

The actual amount of water held in the extracellular reservoir is dependent on the amount of total base (mostly sodium) present.[2b, 15a] The electrolyte concentrations of the intra- and extracellular body fluids are maintained at a remarkably constant level.[2c] Loss of electrolytes with a parallel loss of water from the extracellular fluid compartment does not produce changes in electrolyte concentrations.[13] Only when the extracellular reservoir of base and water is seriously depleted is there a fall in total base concentration in the plasma. The total base concentration by itself, however, gives no indication as to the total amount of base and water lost.

Not only the total base concentration but the relative proportion of acidic and basic constituents is important in a patient with an abnormal loss of fluid containing electrolytes. Such loss of fluid may result in acidosis or alkalosis, in addition to dehydration. Determination of plasma carbon dioxide combining power and plasma chlorides, from which the total base concentration may be approximated, is important in following the patient's electrolyte status.

A detailed discussion of the nutritional requirements of the seriously ill surgical patient will not be attempted here. The importance of an adequate

* Erythrocyte counts or hemoglobin concentrations can be used, but in the present study the hematocrit has seemed to be the simplest way to follow this factor.

intake of carbohydrates and vitamins is well known. Protein metabolism in surgical patients has received wide attention recently. Definite levels of plasma protein are necessary to maintain the plasma osmotic pressure.[16] The rôle of the edema of hypoproteinemia in the prevention of wound healing has been stressed by Ravdin.[17] Because of these considerations, a knowledge of the plasma protein level is important.

The combination of repeated simultaneous hematocrit, plasma protein, carbon dioxide combining power, and chloride determinations gives valuable

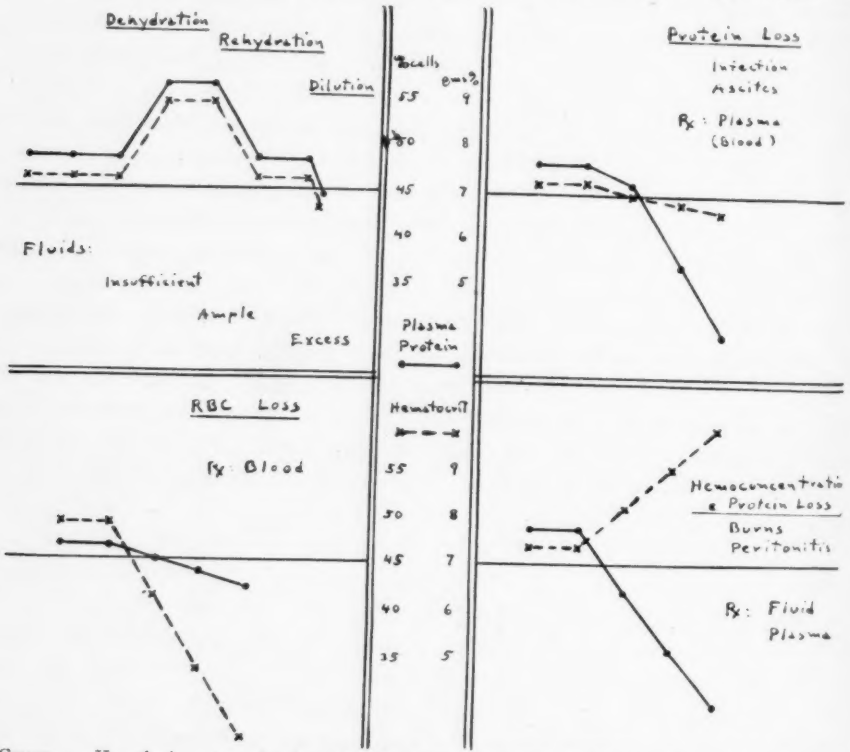

CHART 1.—Hypothetic curves showing the main types of changes in plasma protein and hematocrit values observed in this series.

information for controlling certain types of patients. The main types of variations of plasma protein and hematocrit values (Chart 1) correspond roughly to those which occur in cases of abnormal gastro-intestinal fluid loss, infection, hemorrhage and burns.

The degree of hydration in such cases may be estimated from these four main values, considered together with clinical signs. This is especially helpful when the patient is first seen in a dehydrated state where previous daily total fluid intake and output are not known. When the patient is under observation the daily total fluid balance, intake and output, is followed, water loss from vaporization being estimated. The volume and specific gravity of urine are

also valuable indices. But in the present study the combination proposed above has seemed to give a more reliable indication of the fluid balance in the patient, as well as indicating the erythrocyte and plasma protein levels.

Methods.—The simplicity of making these determinations routinely should be stressed. A single sample of blood, 5–6 cc., drawn without stasis into an absolutely dry syringe, is transferred directly into a Sanford-McGath hematocrit tube containing an adequate amount of heparin. After centrifuging, the hematocrit is read. With a few drops of plasma the protein may be readily calculated from its specific gravity as determined in Barbour and Hamilton's falling-drop apparatus.[18] The remaining plasma is then used for a determination of the carbon dioxide combining power and chloride concentration.

Extracellular electrolyte concentrations have commonly been expressed in a number of different units, such as volumes per cent, milligrams per cent, and equivalents of 0.1 N NaCl. As Gamble[19] and Butler[20] have so clearly pointed out, a complete picture of the electrolyte pattern is possible only if all of its components are expressed in the same unit, preferably milliequivalents per liter.*

Since a solution containing electrolytes is electrically neutral, the equivalent concentration of positive or basic ions must be exactly equal to the equivalent concentration of negative or acidic ions. Therefore the total base concentration may be calculated by an estimation of the total acid concentration. The latter value may be calculated from the plasma carbon dioxide combining power and plasma chloride concentration[15b] by converting these figures to milliequivalents per liter and adding 25 M.eq./L. for the remaining acid radicles, as follows:

CO_2 comb. power	= 60 vol.% × 0.45* =	27 M.eq./L.
Chlorides (as NaCl)	= 600 mg.% × 0.17* =	103 M.eq./L.
"R" ($HPO_4^{=}$, $SO_4^{=}$, organic acid, protein)	=	25 M.eq./L.
Total acid = total base	=	155 M.eq./L.

* Conversion factors for changing the usual units to milliequivalents per liter.

Specimens of urine collected at the same time as the blood sample is taken should be examined for albumin and acetone, and, in the absence of evidence of marked renal damage, ketosis, or hypoproteinemia, "R" may be assumed to equal about 25 M.eq./L.[19] The resultant figure for total base, although not absolutely correct, is sufficiently accurate for most clinical purposes.

Therapy.—The routine just described gives very definite indications as to the type of fluid needed. A low or falling hematocrit value usually indicates the need for whole blood transfusions. A low protein concentration is a prime

* A milliequivalent is the equivalent weight of an ion or molecule in milligrams. For example, one milliequivalent per liter means 23 mg. of sodium ion, 61 mg. of bicarbonate ion or 35.5 mg. of chloride ion, respectively, per liter of solution.

indication for plasma transfusion when the hematocrit value is normal or above normal (as in burns). Protein is supplied while at the same time blood cells are not added to a vascular system already relatively overloaded with them. Maintenance of the plasma protein level with intravenous amino-acids as reported by Elman and Weiner[21] has not been attempted in this study.

Parenteral fluids are given to a great majority of patients according to relatively simple rules. Normal saline (usually containing 5 per cent glucose)

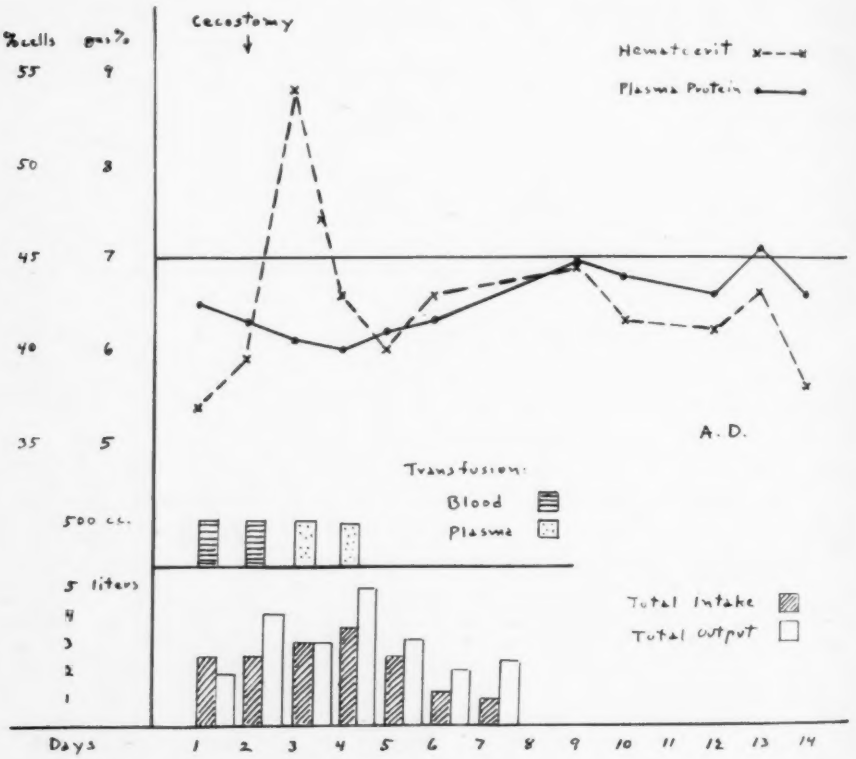

CHART 2.—Case 1: Illustrates the following points:
(1) Marked rise in hematocrit following a negative fluid balance of one day (the day of operation), which suggests previous depletion.
(2) Lack of simultaneous rise of proteins suggesting a loss of protein and indicating plasma transfusion.
(3) Satisfactory postoperative course despite several negative balances.

is given in equal volumes to replace losses of abnormal fluids (gastric, biliary, pancreatic, intestinal) which never exceed physiologic saline concentration, plus an allowance of 1 to 5 Gm. of sodium chloride for urinary excretion. The balance of water for insensible loss, estimated to lie between one and two liters, is given as a solution of 5 per cent glucose in distilled water. Under this regimen most patients showed an adequate urinary output of one liter per day.

The estimation of electrolyte needs in the patient with a serious water and electrolyte depletion has been attempted in several ways. One easy method

is to replace abnormal fluid losses with equal volumes of normal saline,[3] as mentioned above. Another, which in this study has been found to be somewhat unreliable, is to control the salt administration by following the urinary chloride concentration.[5, 6] In cases with marked acidosis, Hartmann[22] has proposed the quantitative use of sodium lactate to raise the carbon dioxide combining power. Coller and coworkers[3] have proposed a formula for replacement of sodium chloride based on the plasma chloride levels. These

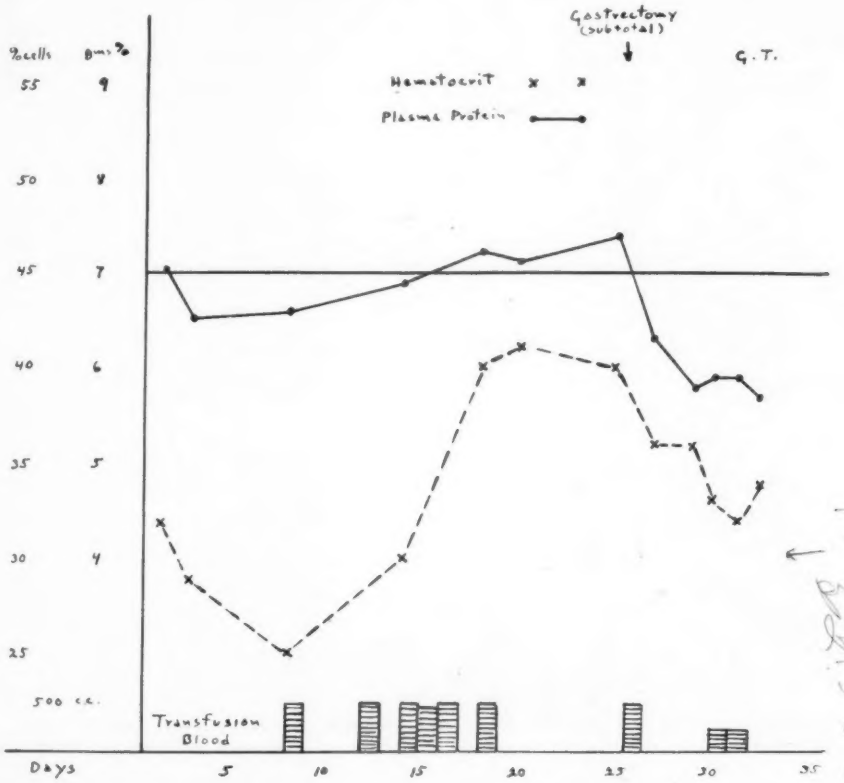

CHART 3.—Case 2: Shows:
(1) Relative hemoconcentration due to dehydration on admission partially concealing an anemia which became more apparent following administration of fluids.
(2) Response of anemia to transfusion.

methods have been unsatisfactory because they ignore total base as such and hemoconcentration as an indicator of serious losses of extracellular water and electrolyte.

In this clinic a formula has been worked out and used which is only a first approximation of the amount of base required. This formula is based on three assumptions: First, that the relative loss of interstitial fluid in dehydration is at least equal to the relative decrease in the plasma volume; secondly, that the electrolyte pattern of the interstitial fluid is qualitatively the same as in plasma; and thirdly, that electrolyte needs calculated from plasma concentra-

tions (corrected for normal plasma volume) may be extended to the entire extracellular volume. This calculated amount of base with an adequate amount of water will restore the depleted extracellular fluid volume to a point somewhat beyond that necessary for maintenance of a normal plasma volume but not necessarily to a normal state.

Because 90 per cent of the base in the extracellular fluid is sodium, all calculations and base replacements may be conveniently referred to the sodium

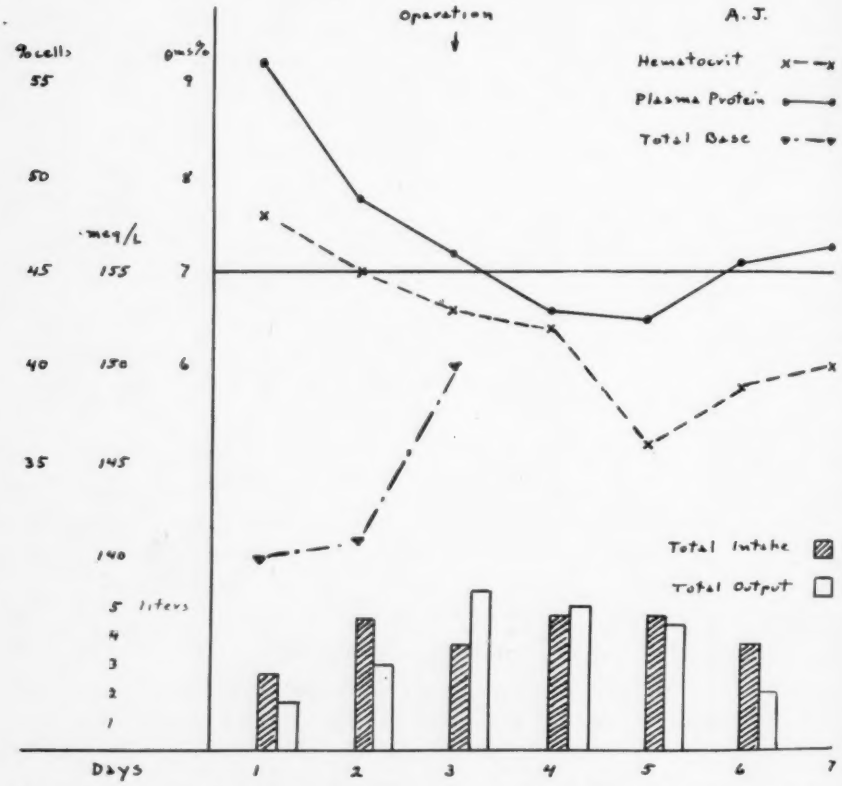

CHART 4.—Case 3: Shows the initial dehydration indicated by a high hematocrit and plasma protein, a low total base, and their response to water and electrolyte therapy.

ion. The calculated sodium ion requirement is given as sodium chloride, sodium bicarbonate, or sodium lactate, according to the requirement for acid ions.

The derivation of the formula follows: The observed concentration of plasma total base in milliequivalents per liter (B) is corrected by the ratio of the plasma protein concentration in grams per cent at normal hydration (Pn) to the observed plasma protein concentration (Po). This value is subtracted from 155, the normal concentration of extracellular total base in milliequivalents per liter. The difference is multiplied by a factor made up of the equivalent weight of sodium, 23, multiplied by 0.2 of the body weight in kilograms (W), which is the approximate fraction of the body made up of extracellular fluid,[10]

multiplied by 0.001 to change milligrams to grams. The result is the grams of sodium ion required.

$$\text{Gm. } Na^+ \text{ required} = 0.0046\ W \left(155 - \frac{PnB}{Po}\right)$$

The same calculation can be made using hematocrit instead of plasma protein values. However, the ordinary hematocrit reading as observed (Ho) and the reading at normal hydration (Hn) are converted to plasma volume and expressed as a ratio of plasma volumes per unit volume of cells, which is the factor desired for correcting the observed plasma total base concentration (B). This ratio is expressed thus:

$$\frac{(100 - Ho)\ Hn}{Ho} \Big/ (100 - Hn), \quad \text{or} \quad \frac{(100 - Ho)\ Hn}{(100 - Hn)\ Ho}$$

The final equation therefore becomes:

$$\text{Gm. } Na^+ \text{ required} = 0.0046\ W \left(155 - \frac{(100 - Ho)\ HnB}{(100 - Hn)\ Ho}\right)$$

The sodium ion requirement can be converted into grams of sodium chloride, sodium bicarbonate, and sodium lactate, by the factors 2.5, 3.6, and 4.9 respectively.

The accuracy of the calculations of the base requirement by either of the above equations depends upon knowing or being able to estimate fairly accurately the hematocrit value or plasma protein concentration at normal hydration. In the anemic patient where the hematocrit value at normal hydration is not known, the plasma protein may offer a more accurate basis for calculation. Where neither the hematocrit nor plasma protein values at normal hydration can be estimated, the formula cannot be used. In such cases more empiric methods are required, such as giving fluids up to 6 per cent of the body weight.

The application of this formula is illustrated in Case 5, L. Del Q., as follows:

Body weight at normal hydration	= 95 Kg.
Initial total base	= 132 M.eq./L.
Initial hematocrit	= 62 per cent cells
Estimated hematocrit at normal hydration	= 40 per cent cells
Calculated sodium ion requirement = $.0046 \times 95 \times \left(155 - \frac{(100 - 62) \times 40 \times 132}{(100 - 40) \times 62}\right)$	= 44.1 Gm. Na^+
Actual amount of base given (net)	= 35.6 Gm. Na^+
Final hematocrit	= 41 per cent cells
Final total base	= 152 M.eq./L.

The results of the application of this formula in a small series of patients are tabulated in Table I. It must be remembered that it is the net sodium ion

requirement being calculated; allowance should be made for simultaneous sodium losses.

TABLE I

RESULTS OF THE APPLICATION OF FORMULA FOR CALCULATION OF THE SODIUM ION REQUIREMENT

Patient	Body Weight at Normal Hydration Kg.	Initial Total Base M.eq./L.	Initial Hematocrit or Protein % Cells Gm.%	Hematocrit or Protein at Normal Hydration % Cells Gm.%	Calculated Base Requirement Gm. Na^+	Actual Amount Base Given Gm. Na^+	Time Interval Hours	Final Hematocrit or Protein % Cells Gm.%	Final Total Base M.eq./L.
L. Del Q.	95	132	62	40	44.1	35.6	48	41	152
A. J.	85	140	9.2	7.0	19.2	17.6	48	7.2	150
J. H.									
Period I	62	134	48	40	16.5	21.0	72	45	145
Period II	62	140	55	40	22.6	17.8	84	38	158
Period III	62	138	52	38	24.5	22.2	72	38	151
F. G.	60	138	37.5	30	15.5	16.3	72	32	164

Although the above formula stresses the need for base, the requirements for acid ions and water must be kept constantly in mind. Electrolyte and water losses in dehydration should be replaced in physiologic proportions. About three-quarters of the total base requirement is usually given as isotonic saline and the remainder as sodium lactate or bicarbonate. In the presence of a lowered carbon dioxide combining power or chloride concentration in the plasma, these constituents must be restored to normal levels by the administration of additional sodium chloride, bicarbonate, or lactate as indicated. Disregard of these precautions in replacing electrolytes may lead to a dangerous alkalosis or acidosis. The sole aim of this procedure is the restoration and maintenance of physiologic concentrations and amounts of basic ions, acid ions, and water.

All efforts to regulate electrolyte and water balance depend ultimately upon the activity of the kidney. This organ must excrete or conserve base in accordance with body needs, dispose of surplus acid ions by forming ammonium salts which appear in the urine, eliminate metabolic waste products, and control the water content of the blood. In performing these functions the kidney in a normal adult produces one or two liters of urine per day. Water deprivation to the point of reduced urine output interferes with renal control of acid-base balance and causes a retention of urea and other products. Correction of acidosis, alkalosis and dehydration with physiologic saline is possible only because the kidney functions properly. Even then, one or two days may be required for the attainment of normal conditions. Definite advantages result from the parenteral administration of electrolytes and water in physiologic proportions and amounts, as recommended in this paper. The acid-base

imbalance is corrected within a few hours. The kidney is spared the burden of eliminating the unnecessary electrolytes.

The use of the values—hematocrit, plasma protein, and total base estimated from chloride and bicarbonate—is illustrated in the appended ten cases.

In the charts, a base line is drawn at 7 Gm. per cent and 45 per cent cells as a simple convenience. Actually there should be "a normal zone" between 6 and 8 Gm. per cent and 40 and 45 per cent cells. As regards intakes and outputs, the total intake includes all oral and parenteral intake. The total output includes urine, vomitus, any drainage from the gastro-intestinal and biliary

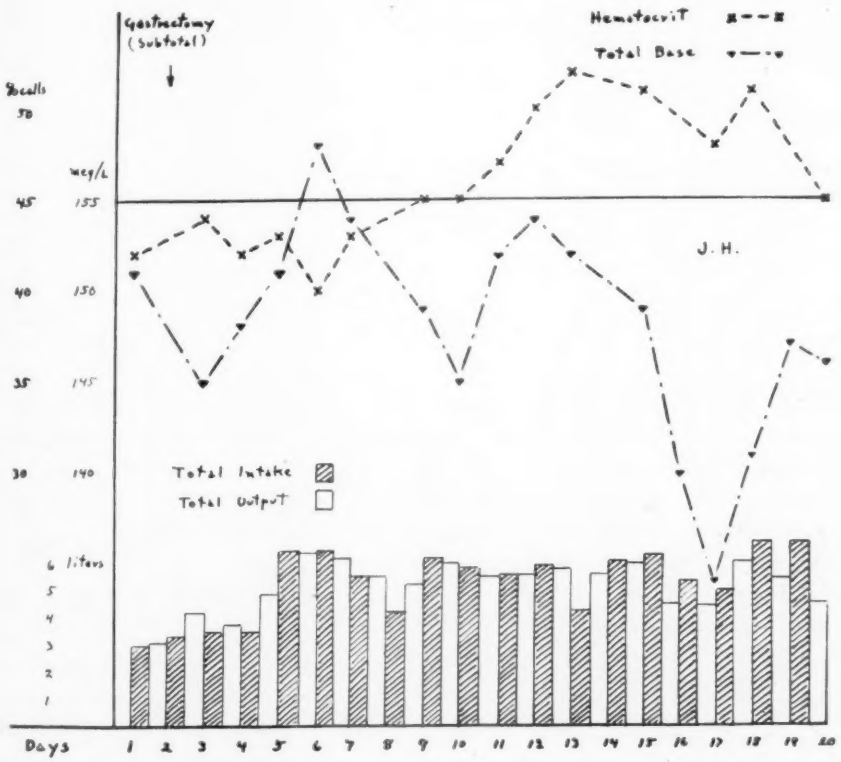

CHART 5.—Case 4: Shows the first 20 postoperative days and illustrates the slow building up of a negative fluid balance; a diminished fluid reserve is indicated by a rising hematocrit before the total base falls to significantly low levels.

tracts, and water of vaporization which is approximated between one and two liters, depending on the patient's size, temperature, and the weather. The probable error in the total output is at least 200 cc.

ILLUSTRATIVE CASE REPORTS

Case 1.—A. D., Negress, age 57, had been vomiting and showed signs of intestinal obstruction of one week's duration. A cecostomy was performed for large bowel obstruction due to carcinoma of the descending colon. The carcinoma was later removed by the Mikulicz procedure (Chart 2).

Case 2.—G. T., white, male, age 49, was diagnosed as having a carcinoma of the stomach. Following a period of building up of the red cell level, a subtotal gastrectomy was performed. Convalescence was satisfactory (Chart 3).

Case 3.—A. J., Negress, female, age 40, had had vomiting, obstipation and abdominal distention for three days. At operation an adhesive band constricting the terminal ileum was released. Convalescence was uneventful (Chart 4).

Case 4.—J. H., Negro, male, age 54, had had a subtotal gastrectomy performed for a gastric ulcer, which was followed by complete and partial obstruction caused by post-

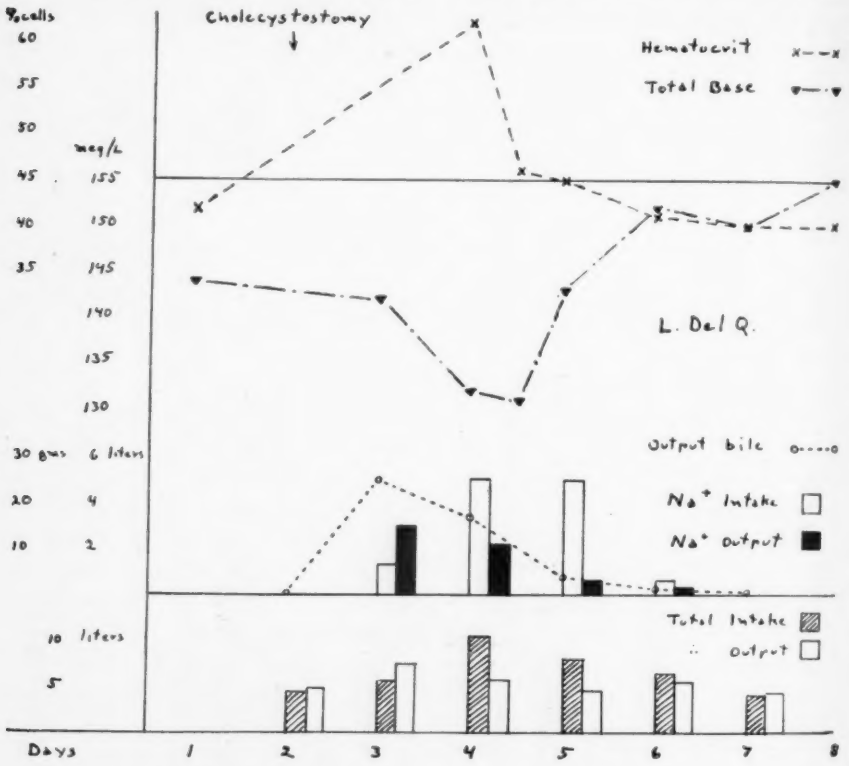

CHART 6.—Case 5: Shows:
(1) Rapid and severe dehydration due to a sudden excessive loss of sodium salts and water.
(2) The moderate reduction in total base level is deceptive because it does not indicate the enormous loss of electrolyte, recognizable only by considering hemoconcentration in conjunction with total base level.
(3) The hematocrit first indicating a satisfactory response to therapy while the total base still remained low.
(4) The positive sodium ion balances necessary to restore the patient to completely normal levels.

operative adhesions for 40 days, necessitating a second celiotomy and jejunostomy. During this time he was sustained entirely by parenteral therapy. Subsequent recovery.

Case 5.—L. Del Q.,* white, female, age 42, suffered from diabetes, severe obstructive jaundice and pain. Cholecystostomy performed and a common duct stone was subsequently passed. Between the twelfth and thirty-sixth postoperative hours 5,000 cc. of bile drained externally, and patient became severely dehydrated and anuric. She responded to massive parenteral therapy. Convalescence was uneventful (Chart 6).

* We are indebted to Elizabeth Dudley, B.S., M.S., Department of Pediatrics, School of Medicine, University of Pennsylvania and the Children's Hospital of Philadelphia, for the sodium determinations on this patient.

Case 6.—H. B., white, male, age 33, had had a liver abscess aspirated at celiotomy, with subsequent peritonitis and death. Autopsy revealed very extensive multiple liver abscesses and fluid in the abdominal cavity (Chart 7).

Case 7.—H. W., white, male, age 58, had had a posterior gastrojejunostomy performed for obstruction of the duodenum due to carcinomatosis. Postoperatively, the patient bled from his stoma and, despite a reoperation, died (Chart 8).

Case 8.—J. P., Negro, male, age 43, sustained first and second degree burns of both lower arms and hands. Treated locally with tannic acid and silver nitrate. Subsequent convalescence was uneventful, and no skin grafts were necessary (Chart 9).

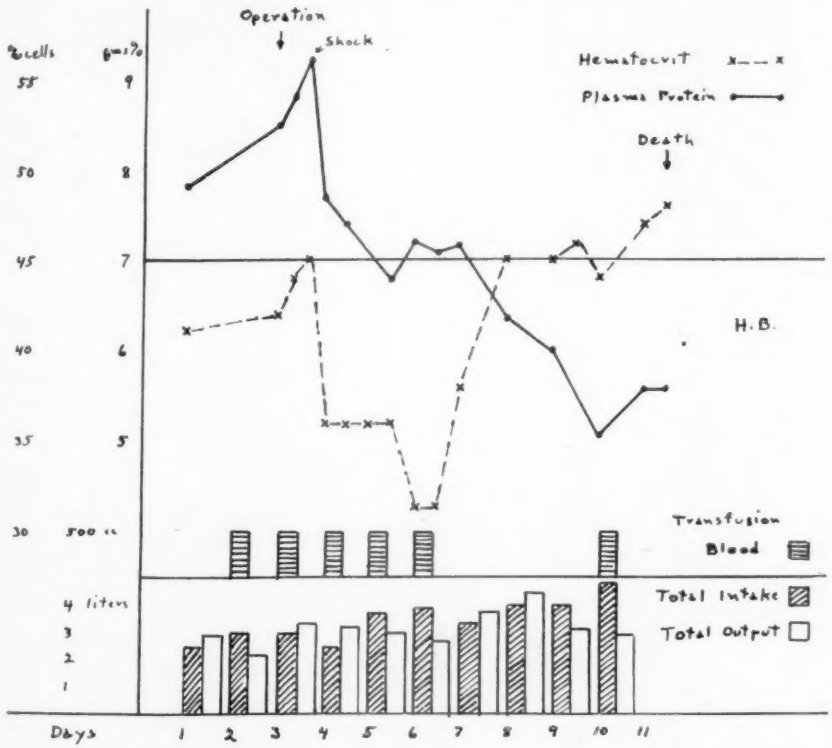

CHART 7.—Case 6: Shows:
(1) The extremely severe shock immediately after operation and the response to therapy.
(2) The secondary dehydration as evidenced by the rising hematocrit.
(3) The marked loss of protein when at the same time the hematocrit was rising. Plasma transfusions should have been given during this period.

Case 9.—J. C., white, female, age 14, sustained second and third degree burns of entire back, buttocks, posterior surface thighs, and right hand (20 to 25 per cent of the body surface). Treated locally with tannic acid and silver nitrate. Systemic reaction fifth and sixth days. Recovery without skin grafts (Chart 10).

Case 10.—A. R., white, male, age 25 months, sustained second and third degree burns over entire back and most of chest and abdomen. Immediate tanning with tannic acid and silver nitrate and subsequent skin grafting. Acutely toxic and moribund on third day, with improvement following the administration of adrenal cortical extract (Chart 11).

Discussion.—Strict control of electrolyte and water balance was necessary in less than 10 per cent of the surgical patients in the wards of the Penn-

sylvania Hospital. Studies were begun on admission of every patient showing clinical signs of dehydration, intestinal obstruction, or severe burns, and also on those patients in whom extensive surgery of the gastro-intestinal tract was anticipated. Prolonged biliary or gastric drainage was considered an imperative indication for electrolyte and water balance control. Prompt quantitative replacement of the proper fluids has reduced the expected mortality rate and facilitated recovery in many instances.

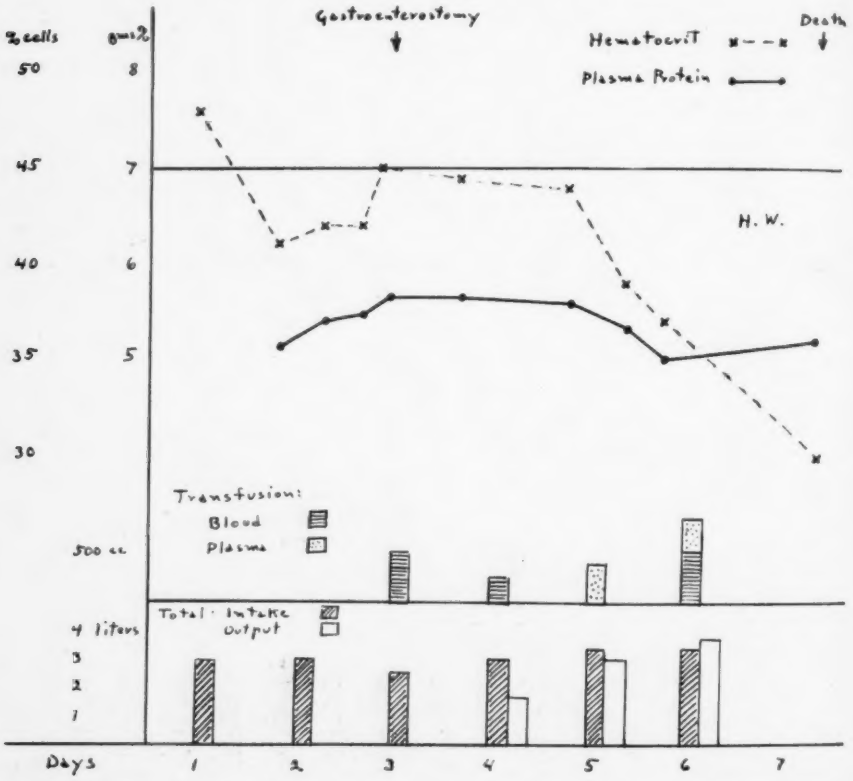

CHART 8.—Case 7: Illustrates the occult hemorrhage, revealed by the falling hematocrit while the protein level was being maintained. Hemorrhage was subsequently confirmed by tarry stools.

Every patient was an individual problem, and, while the general trend of values followed the types shown in Chart 1, the time relations and magnitude of changes varied from patient to patient. The particular determinations made on a given patient depended upon the physiologic problem involved, and the kind and quantity of parenteral medication had to be redetermined at frequent intervals.

There seems to be some justification in presenting another formula for calculating electrolyte requirement. The emphasis should be shifted from neutral salt to total base, which is the factor that determines the amount of water held in the tissues. Analyses will indicate the appropriate acid ion,

bicarbonate, chloride, or lactate, for balancing the base given. Formulae proposed by other authors have neglected the factor of hemoconcentration, not only as an indicator, in itself, of loss of extracellular water, but as a clue to loss of extracellular base not shown by plasma electrolyte concentrations. Even with this correction the formula (as with those proposed by others) suffers from the fact that the actual or optimal volume of the interstitial reservoir is not accurately known. For practical purposes our calculations

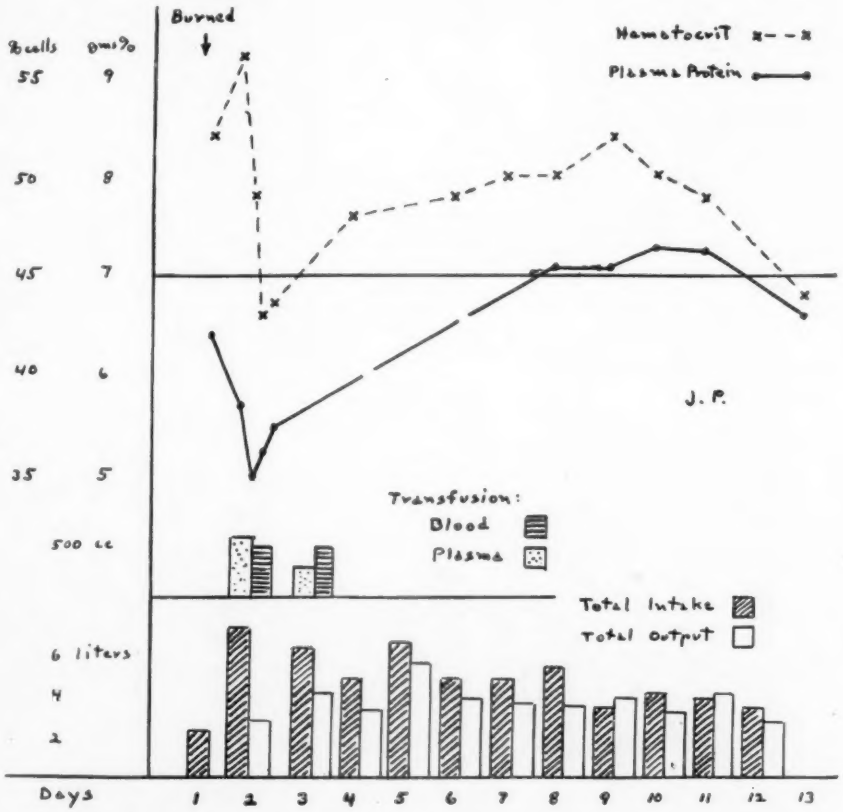

CHART 9.—Case 8: Shows:
(1) The early marked loss of protein at the same time that the blood is rapidly concentrating—a prime indication for plasma transfusion.
(2) The response to therapy evidenced by hemodilution and rise of the plasma protein level.
(3) The severe systemic disturbance that may follow a relatively small burned area.

have been based on the assumption that total extracellular fluid volume amounts to 20 per cent of the body weight. However, the use of these approximate calculated values marks an advance over arbitrary rules so prevalent in the early days of parenteral therapy.

Unavoidable difficulties arise in the control of water and electrolyte balance in patients with anemia, hypoproteinemia, and cardiovascular or renal disease. Although establishing a base-line in patients with a deficiency of erythrocytes or plasma protein is merely a guess, serial determinations in this type of patient

are valid. In patients with cardiovascular disease the route and rate of parenteral administration of fluids must be modified in order to avoid circulatory embarrassment. The damaged kidney, in many instances, is unable to conserve base and eliminate acid ions preferentially, or to handle large quantities of electrolytes. In those patients with low levels of plasma protein, the administration of the calculated quantity of electrolyte may produce edema.

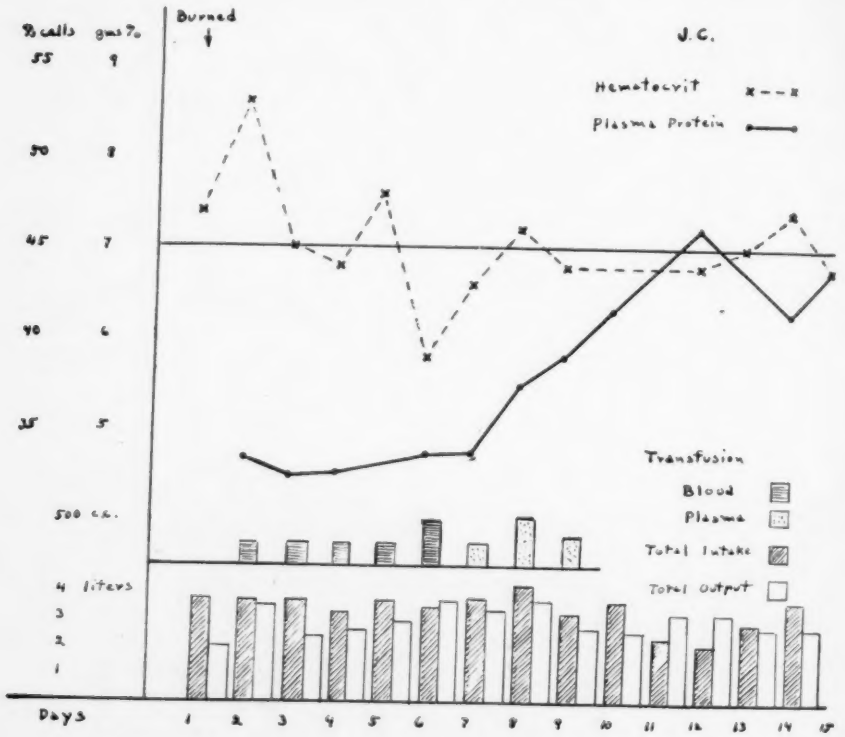

CHART 10.—Case 9: Shows:
(1) The early hemoconcentration with the marked loss of protein.
(2) The rise in plasma protein following the initiation of plasma transfusions.

Furthermore, patients losing large amounts of protein through the kidney seldom benefit from plasma transfusion.

CONCLUSIONS

Electrolyte and water balance in surgical patients may be evaluated fairly accurately by simultaneous determinations of hematocrit value, plasma protein, chlorides, and carbon dioxide combining power. From the two latter figures the total base is approximated. Hemoconcentration, as shown by a rising hematocrit or plasma protein value, is an indication of serious depletion of the extracellular water. A falling total base concentration indicates serious extracellular base depletion, and, when corrected for hemoconcentration, may be used to calculate the amount of base required.

The analytic results also indicate the type of parenteral fluid needed, either whole blood, plasma, physiologic saline, bicarbonate and lactate, or glucose in distilled water. Such a routine has been found valuable in those patients presenting serious problems of fluid balance.

The authors wish to thank Dr. Walter E. Lee and Dr. John B. Flick for their encouragement and for access to the patients on their Services; and to acknowledge the assistance of Miss Marian Janney, and of the hospital clinical and laboratory staffs. The

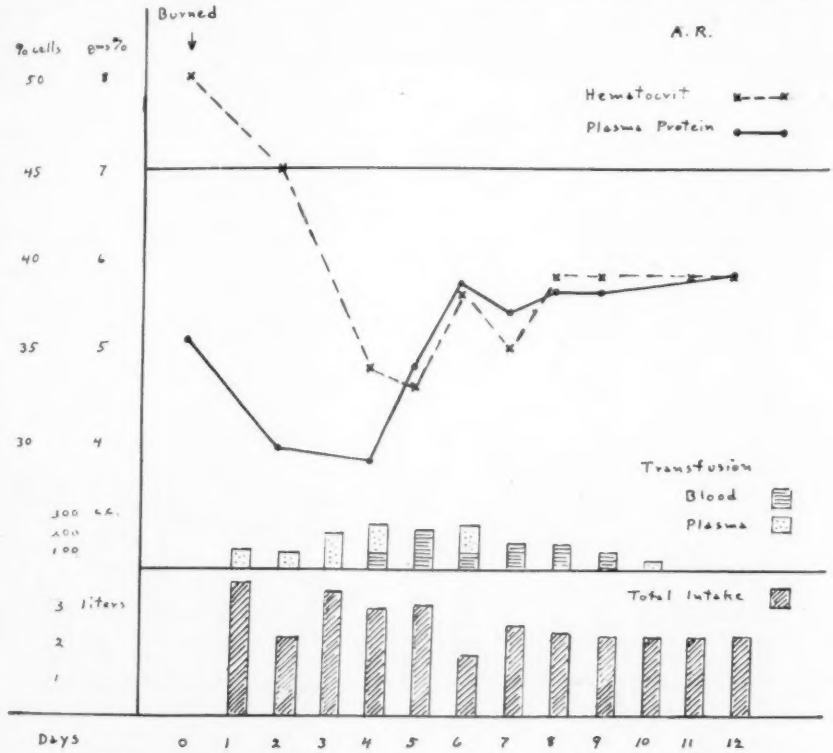

CHART 11.—Case 10: Shows:
(1) The very marked protein loss in the presence of hemoconcentration.
(2) The hemodilution in response to plasma transfusions and parenteral fluid with maintenance of the protein level.
(3) The substitution of blood for plasma when the hematocrit fell well below normal, and a satisfactory response in hematocrit level.

authors are also indebted to Drs. John Scudder and C. R. Drew of Presbyterian Hospital, New York City, for demonstrating the hematocrit and plasma protein methods and results on their patients.

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THE COMBINED USE OF ZINC PEROXIDE AND SULFANILAMIDE IN THE TREATMENT OF CHRONIC, UNDERMINING, BURROWING ULCERS DUE TO THE MICRO-AEROPHILIC HEMOLYTIC STREPTOCOCCUS*

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THE SUCCESSFUL treatment of chronic undermining, burrowing ulcers with zinc peroxide has been reported in four previous communications[1,2,3,4] and has been confirmed by several other authors.[5,6,7] These infections are being seen and recognized with increasing frequency, but there is still undue delay in their diagnosis and in the institution of proper treatment. The

FIG. 1.—Case 1—on admission: Note the extensive undermining of the skin and in between the femur and the hamstring muscles. The saphenous vein is intact but thrombosed. There is no gangrene of the skin. There is an almost 90° contracture of the knee.

chronicity as well as the extent of these extraordinary defects in the surface of the body renders them certain to be contaminated with many different species of bacteria. Some of these organisms are mere contaminants and are present in small numbers only. Others find the surface exudate suitable for rapid multiplication, but they do not penetrate the tissues. Still others are able to invade the deeper tissues of the body and take part in the infection

* Read before the American Surgical Association, Hot Springs, Va., May 11, 12, 13, 1939.

itself. For these reasons, a number of different organisms which have frequently been found to be associated with these ulcers have been considered

FIG. 2.—Case 1—19 days after excision and before skin graft: New epithelium is growing in at the margins. The cavity beneath the femur is smaller. An attempt was made to save a skin flap for the groin, but this was not worth while. No activity of infection developed at the site of ligation of the saphenous vein near the femoral.

FIG. 3.—Case 1—26 days after excision; seven days after skin graft: Some of the grafts have fused with each other and with the marginal epithelium.

the etiologic agents when the really significant organism has not been obtained on culture. The essential organism has frequently been missed simply

because, in the great majority of hospitals, bacteriologic studies are limited to simple aerobic cultivation on routine media.

We have had the opportunity of studying over 40 of these unusual infections. By careful anaerobic as well as aerobic studies, we have invariably

FIG. 4.—Case 1—45 days after excision; 26 days after skin graft: The area is almost covered with epithelium. The cavity beneath the femur is smaller. Extension of the knee approximates 135°.

FIG. 5.—Case 1—80 days after excision; 10 days after complete healing: Extension of leg is about 150°.

found the micro-aerophilic hemolytic streptococcus to be present. In many instances, it has been found in pure culture, when specimens of exudate have been taken from the deep sinuses or from far beneath the undermined skin

FIG. 6.—Case 2—just before operation: Note the ulceration extending over but not exposing the thyroid cartilage. Undermining extends down to the clavicle and up to the mandible. Lymph nodes on the jugular vein at the angle of the jaw and in the tip of the parotid were involved and were removed.

FIG. 7.—Case 2—late result; seven months after complete healing: The only Thiersch graft case in the series. The skin moves freely over the thyroid cartilage and movements of the neck are only slightly restricted.

FIG. 8.—Case 4—on admission: Note the shaggy base of the ulcer on the arm and the extensive undermining with daughter ulcerations forming as perforations from beneath. The axillary ulcer is smaller though older and two sinuses extend upward to the lymph nodes. No gross connection could be found between these ulcers, and the arm lesion may have resulted from inoculation of the surface.

FIG. 9.—Case 4—three months after excision; one month after complete healing: Abduction of arm only slightly limited. Scar soft and pliable.

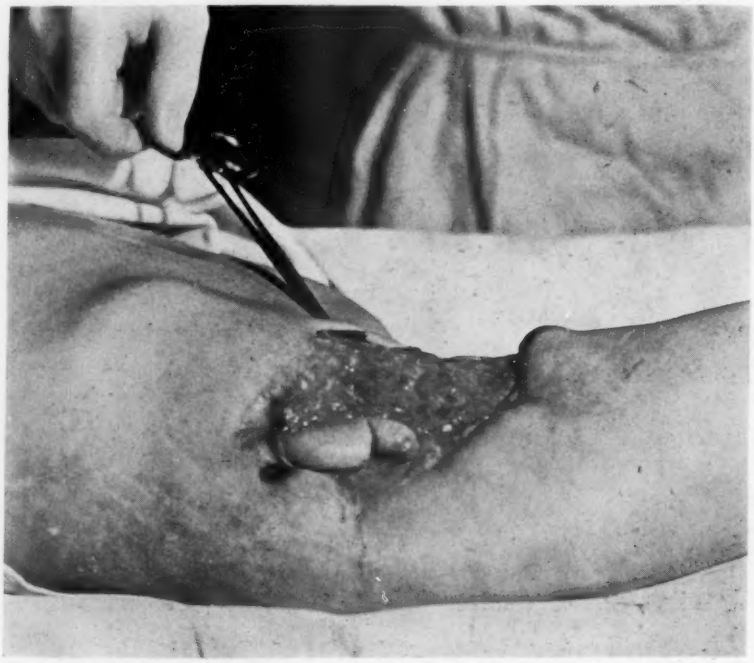

FIG. 10.—Case 6—on admission, about two weeks after zinc peroxide had been used. It is obvious that adequate contact was not possible in certain areas. A skin bridge between a daughter ulcer and the main ulcer is shown. A skin flap which had been left has curled up and there is active infection at its base.

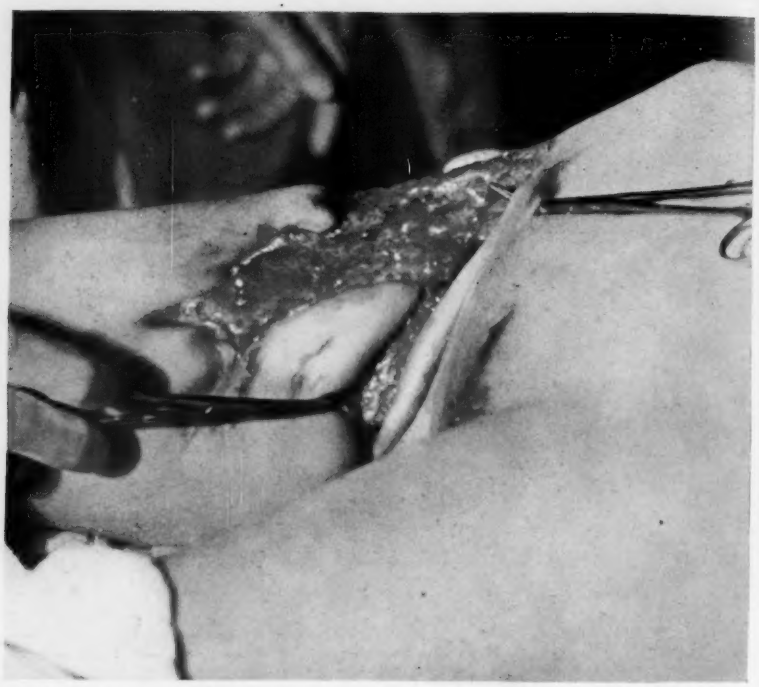

FIG. 11.—Case 6—on admission: Note the skin bridges and the rolled-in, undermined margins.

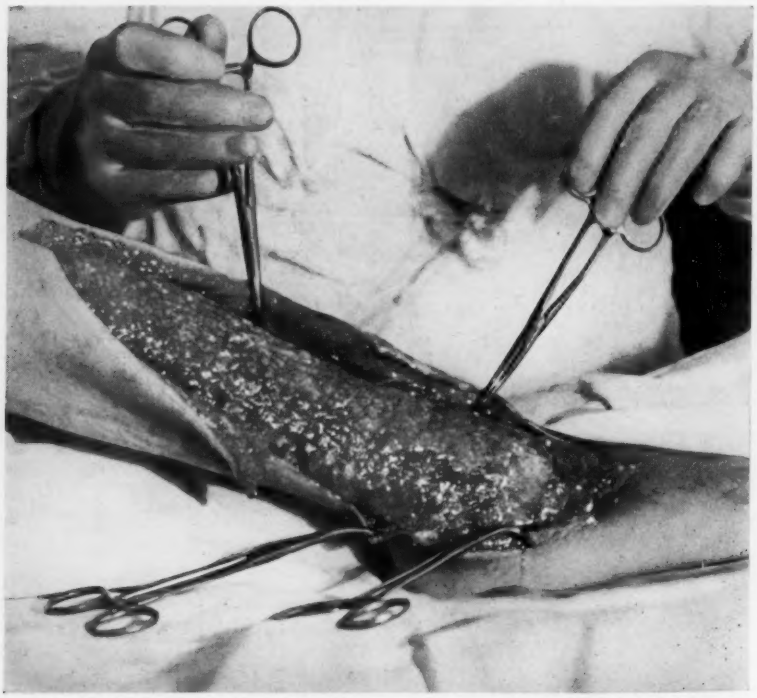

FIG. 12.—Case 6—on admission: The flaps are extensively undermined. The tip of the upper clamp enters a small perforation of the skin from beneath. There are two other areas of activity below where adequate contact had not been possible.

flaps where the inflammatory process is often most active. On certain occasions, also, during the course of treatment, when the organisms have been largely removed from the wound, some little area of recurrent activity has

FIG. 13.—Case 6: Healing complete 39 days after excision and 29 days after skin graft. There had been a little mechanical erosion of the marginal epithelium which promptly healed over.

shown the reactivation or persistence of this organism. Therefore, even though we have not been able to produce this disease in animals and thus fulfill Koch's postulates for the final proof of etiology, we feel confident that

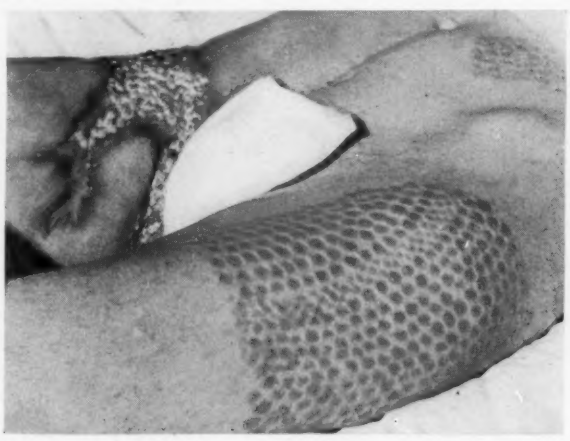

FIG. 14.—Case 6—time same as in Figure 13: Healing complete of doning and receiving areas.

its invariable presence, at times in pure culture, establishes it as the etiologic agent for this clinical entity, and we believe that the failure of others to find this organism in these lesions can be traced to faulty or inadequate methods of bacterial cultivation.

Laboratory studies with these organisms have shown them to be micro-

FIG. 15.—Case 6—time same as in Figure 14: Healing of leg complete. There is a slight degree of foot drop.

aerophilic hemolytic streptococci lying intermediate between the aerobic hemolytic streptococci and the strictly anaerobic hemolytic streptococci, pre-

FIG. 16.—Case 14—on admission: Note the relatively small ulceration in the axilla. Two sinuses have burrowed through the pectoral muscles from beneath.

ferring for their multiplication a reduced oxidation-reduction potential in their environment. When they are in this state, they have certain under-

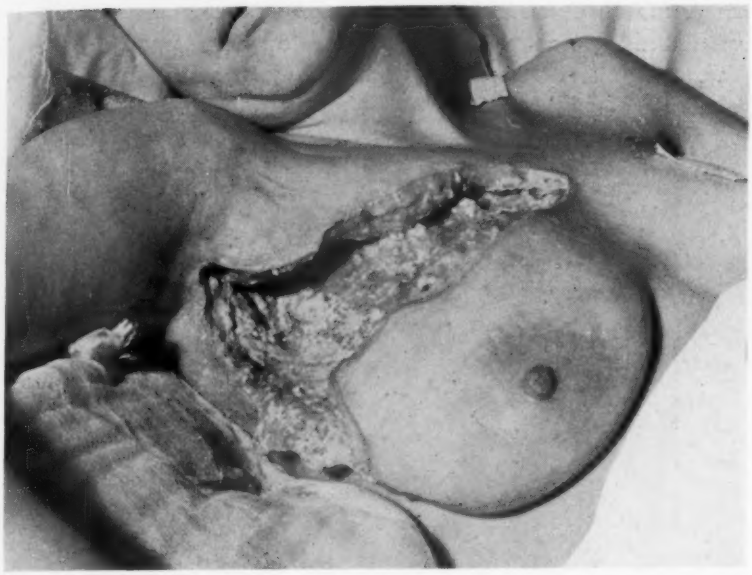

FIG. 17.—Case 14—three days after complete excision of the diseased tissue: Zinc peroxide is adherent to freshly cut surface. No repair as yet. Patient prostrated by high temperature and in delirium, both of which ceased on withdrawal of sulfanilamide.

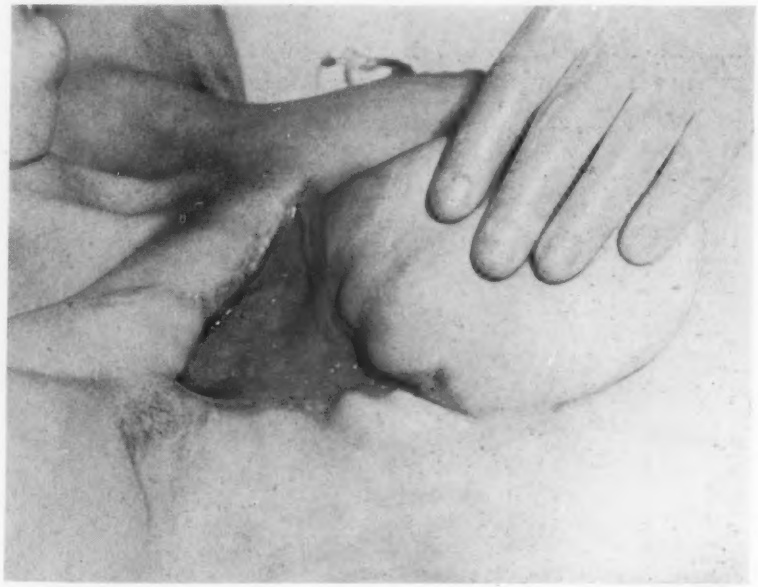

FIG. 18.—Case 14—29 days after excision just before skin graft: Good granulating surface. Edges are adherent and new epithelium is growing in.

mining, burrowing propensities, which may be linked up with their preference for a partially anaerobic environment. After a few transplantations on artificial media, these organisms can be made to grow readily under ordinary aerobic conditions. When this has occurred, the usual tests applied for the

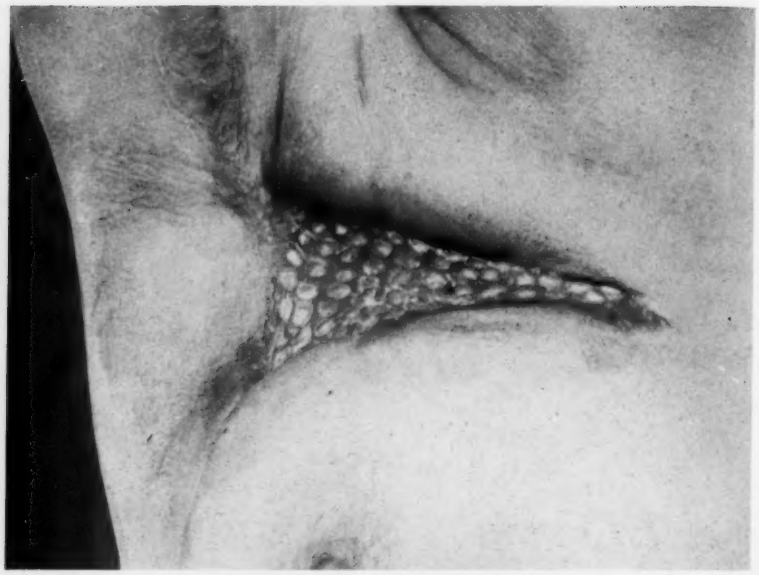

FIG. 19.—Case 14—41 days after excision, 12 days after skin graft: Healing complete. Abduction of arm only slightly limited.

FIG. 20.—Case 15—on admission: Chronic infection of 19 years' standing has resulted in redundant folds of skin overlying a maze of sinus tracts undermining the skin and extending up to axillary nodes.

differentiation and classification of hemolytic streptococci do not show any significant differences between these organisms and aerobic hemolytic streptococci obtained from other human lesions. All that we have tested fall into

Lancefield's[8] Group A and into heterogeneous groups according to fermentation reactions or agglutination tests.

For this reason, when sulfanilamide was found to act favorably in ordinary hemolytic streptococcus infections, this drug was applied in instances of

FIG. 21.—Case 15—on admission: A condition similar to that involving the axilla in the right groin and scrotum.

these lesions also. Sometimes this drug has been used in the treatment of these cases by doctors who have not taken the trouble, or have not had the facilities, to make bacteriologic studies. We have attempted to employ it in the treatment of the last 20 cases, which have come under our care after thorough bacteriologic studies had been made. In these cases, we have used sulfanilamide either alone or in conjunction with zinc peroxide.

The use of zinc peroxide has certain disadvantages because its activity

FIG. 22.—Case 15—13 months after final healing, which was complete in seven weeks after operation: Right axilla. Cavity lined with epithelium. Scar somewhat keloidal—softened by radiotherapy. Abduction only slightly limited.

FIG. 23.—Case 15: Left axilla of case shown in Figure 22.

FIG. 24.—Case 15: Thirteen months after final healing of perineum, which was complete seven weeks after operation.

depends upon its close application to the infected tissues. These may be deep under skin flaps or deep down in sinuses or in the center of lymph nodes. In most cases, this requires a preliminary surgical procedure, in order to expose these tissues in such a manner that the zinc peroxide can be properly applied. It would obviously be of great advantage if some medication could be introduced into the body through the circulation, which would reach the advancing margin of the infection either under the skin or deep down in the tissues.

Sulfanilamide acts most dramatically in the early stages of an acute infection caused by the hemolytic streptococcus where there is a condition of cellulitis without any necrosis of tissue, where the blood supply has not been shut off by thrombosed blood vessels and where the drug can diffuse out into the tissues and come in close contact with the organisms. Where there has been a necrosis of tissue or abscess formation,

FIG. 25.—Case 16—on admission: Note the relatively limited undermining. However, the degree of induration around the lesion prevents adequate contact by zinc peroxide without preliminary excision.

FIG. 26.—Case 17—29 days after excision, 18 days after skin graft: Epithelization is complete. The new epithelium is cyanotic from too rapid dependency which should have been avoided.

FIG. 27.—Case 17: Six months after complete healing.

the curative effect with sulfanilamide is definitely limited and surgical drainage with liquefaction and removal of the dead tissue is required before healing can take place.

FIG. 28.—Case 19—on admission: Breast is completely undermined and hanging by two pedicles, with an ulcer in between and on either side.

Lockwood,[9] in 1938, reported his experiences with sulfanilamide in hemolytic streptococcus infections and showed that the presence of peptones markedly interfered with the bactericidal action of sulfanilamide on the hemo-

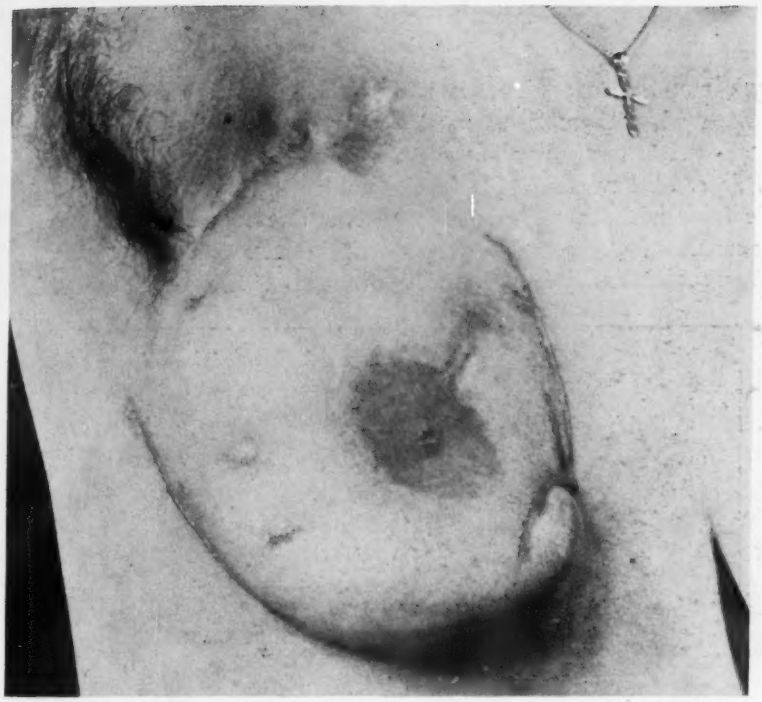

FIG. 29.—Case 19: One month after final healing, which was accomplished in four months.

FIG. 30.—Case 20—on admission: Note the relatively small ulcerations. There was extensive undermining and induration with multiple cribriform sinus openings.

lytic streptococcus. This may explain the relative inefficiency of the drug in chronic streptococcus infections and in the late stages of acute or subacute infections when there is a considerable amount of necrotic tissue in which the split products of protein, such as peptones, are present in large amounts. Swift,[10] *et al.* have found that sulfanilamide has not been effective in rheumatic fever and other subacute or chronic streptococcus infections and that toxic manifestations are more frequent in these cases. Recent work by Fox[11] *et al.* on sulfanilamide from the viewpoint of oxidation-reduction potentials of

FIG. 31.—Case 20—21 days after excision, two days after skin grafting: All but two or three grafts have become adherent.

the environment and the electrical reactions of streptococci suggests that a lowering of the oxidation-reduction potentials towards anaerobic conditions or the lowering of the iso-electric point of the bacteria may interfere with the bactericidal action of sulfanilamide. It is to be expected, therefore, that there might be limitations or difficulties in the administration of sulfanilamide in cases of undermining, burrowing ulcer.

However theoretical these considerations may be, it was only by practical experience that the relative value of these two drugs could be determined, and the steadily increasing number of the cases that have come under our observation in the last few years has given us an unusual opportunity for this study.

The 20 cases included in this report do not differ fundamentally from those previously described. They fall into the three main groups: (1) Postoperative; (2) lymph node involvement; and (3) secondary contamination of an accidental wound or a previously existing infection. Our experience with these cases has confirmed our previously stated opinion that the organism is a hemolytic streptococcus, which has become adapted to an anaerobic

FIG. 32.—Case 20: Six months after final healing.

environment either while residing in the intestinal tract or vagina of the patient or while smoldering in a lymph node.

Each case has certain features of its own and at the same time shows the fundamental characteristics of the disease entity. In certain areas where the skin is thick and probably resistant to necrosis, the burrowing propensities of the organism outweigh the ulcerating propensities. These regions are the perineum and buttocks, vulva, scrotum and axillae. Here multiple sinuses are common and ulceration is generally limited.

The secret of success with zinc peroxide depends upon three fundamental requirements, and the treatment of the cases which have come to us from other doctors who have employed zinc peroxide unsuccessfully has been at fault in

one of these three categories. The first is the material itself. The Du Pont Chemical Company, which manufactured the zinc peroxide originally used and found to be effective, has been the only chemical company consistently able to manufacture effective material. The Merck and Mallinckrodt Companies have tried to do so, but have failed and are now planning to distribute the Du Pont product under its distinctive name, "Z. P. O." A number of doctors who have attempted to use zinc peroxide in the treatment of these ulcers, even among our own acquaintances, have simply asked their pharmacies to obtain some zinc peroxide without specifying the source. They have then been given either the Merck or Mallinckrodt material and have used it without obtaining satisfactory results. The importance of certain physical properties of this material are of fundamental importance because while the chemical content of zinc peroxide in the powder may be high, the oxygen may not be mobilized or made available. The preliminary heating in a dry oven at 140°C. for four hours not only sterilizes the powder, but mobilizes the oxygen. When added to sterile distilled water, after the sterilization and activation process, effective material always flocculates quickly as a soft, curdy mass, leaving a clear supernatant fluid, and it is soon lifted up by the formation of oxygen bubbles. This test should always be made before using any particular preparation.

The second most important feature of the treatment is to obtain close contact between the zinc peroxide and the infection. With many of these ulcers, there are deep, undermined skin flaps and deep sinuses which prevent close contact of the medication unless there has been a preliminary operative procedure undertaken in order to expose the advancing margins of the infection. In many cases, it is obvious when the patient first comes to the doctor that this must be done and it should be done without delay. In other cases, where there is no obvious necrosis of the subcutaneous tissue or induration of the margin, it may be wise to treat the lesion conservatively for a period of a week or ten days. At the end of that time, it will be clear whether or not adequate contact with the material has been obtained, because in those areas where adequate contact has been made, bright red granulations will grow up and if the margin is attached, new epithelium will grow in. In those areas where there is no subsidence of the infection or evidence of repair, it it reasonably certain that the zinc peroxide is not coming into adequate contact and these areas must be exposed or excised.

The third essential feature of the treatment is the prevention of evaporation. The oxygen is conveyed from the zinc peroxide to the tissue by means of water. When zinc peroxide is suspended in water, oxygen is given off into the water, hydrogen peroxide is formed and the oxygen is then transferred to the environment. This leaves H_2O, which then takes up more oxygen from the zinc peroxide. If the zinc peroxide dressing is allowed to dry, this action stops or is greatly diminished and the dry material may mechanically irritate the wound whenever the patient shifts his position. The tissue fluids and the body exudates may act as catalytic agents, but the activity of the zinc peroxide suspension is at its best only when extraneous moisture

is present. For that reason, the zinc peroxide must not only be applied to every part of the wound surface, but the wound surface must then be covered with a double layer of fine meshed gauze soaked in the suspension. This helps to maintain contact, but must, in turn, be covered by gauze compresses or sheet cotton wet with water. The whole dressing is then sealed with vaselined gauze or, better still, gauze impregnated with zinc oxide ointment, which is more impermeable to the air and does not irritate the surrounding skin. This impermeable covering should have a wide margin around the wet compresses, so that slight movement of the part will not displace them. In leg or forearm ulcerations, it is possible at times to use rubber sheeting to seal the dressing, but this is not practical on other parts of the body.

When these three features of the treatment have been carried out, it has been invariably successful, and in the last 20 cases there have been no fatalities. Of these 20 cases, one received zinc peroxide alone, one received sulfanilamide alone, and the other 18 received both. In eight, the sulfanilamide was employed before the zinc peroxide; in eight, in conjunction with zinc peroxide, both forms of treatment starting at the same time; and in two after the treatment with the zinc peroxide had been begun.

Of eight cases in which sulfanilamide was used before the zinc peroxide, there was no evidence whatever of any favorable effect in seven. In one case, in which we were determined to give sulfanilamide a prolonged trial, there was a temporary improvement, but after several weeks, progress came to a standstill. Then the infection became active again even with continued medication.

In eight cases, the sulfanilamide and zinc peroxide were begun at the same time. In one of these patients in whom the infection had entered through a draining sinus from a tuberculous hip and had then produced extensive superficial ulceration with undermining, because of the impossibility of intimate contact, the zinc peroxide was used for only a brief period. Improvement continued with the use of sulfanilamide and the ulcer finally healed leaving, however, the tuberculous sinuses which are still draining, two years later. Credit in this case must be given wholly to the sulfanilamide. Two other cases in this group were given sulfanilamide along with the zinc peroxide treatment without discomfort and possibly with some benefit. Two others took the sulfanilamide for 14 and 19 days, respectively, but asked to have it stopped because of a disturbance of digestion. Withdrawing the drug had no effect on the progress of healing. In the other three patients of this group, the drug was highly toxic; one was delirious for five days, the other for four days. One of these had to be restrained. Reason was restored in both cases promptly after withdrawal of the drug. The third was extremely nauseated and ran a high temperature for four days. Both symptoms promptly disappeared when the drug was stopped.

Of the two remaining cases which received sulfanilamide sometime after the administration of zinc peroxide, in one, the healing process seemed to show a definite spurt when sulfanilamide was given, but it had to be discon-

tinued after four days because of nausea and anorexia. In the other case, there was induration of the margin which had not been brought under control with the zinc peroxide because the preliminary operative procedure did not permit adequate contact. To obviate further operation, sulfanilamide was tried and the infection then came definitely under control.

Mention should now be made of the control cases—one receiving sulfanilamide alone and the other zinc peroxide alone. The first patient had an ulcer beneath the breast of nine months' standing. Six operations had failed to halt the progress of the infection. Sulfanilamide was started and in six days there was striking improvement. It was discontinued for seven days and the activity of the infection recurred. The drug was readministered with steady improvement and final healing, but it took 20 weeks from the time of admission. The other patient had a lesion of the buttock and perineum involving the anus, of four years' duration. It was excised and zinc peroxide was applied. Skin was grafted on the nineteenth day and it was completely healed in 40 days. When the other 18 cases are considered with them, it may not be far wrong to consider these last two cases as representative of the relative value of these two forms of treatment in chronic, undermining, burrowing ulcer. It is possible for sulfanilamide to result in the healing of certain of these cases without the use of zinc peroxide. This is not only illustrated by one of our cases (Case 19), but it has been reported by others.[12] However, the process of healing was very much longer than in the cases treated with zinc peroxide alone or with a combination of the two forms of treatment.

BRIEF SYNOPSES OF THE 20 CASES TREATED

Cases Receiving Sulfanilamide Before Zinc Peroxide

Name Hist. No.	Location	Type	Duration of Disease	Period of Treatment	Course
Case 1 H. K. 521,038 Adm. 5-28-37 Disch. 8-19-37 (Figs. 1, 2, 3, 4 and 5)	Leg and thigh	Contam. Abscess	6 mos.	11 wks.	*Before admission:* Multiple boils 2 yrs.—one on leg took on new aspect with ulceration, undermining up inner surface of thigh to groin. Burrowed beneath bone to outer surface of thigh. Given sulfanilamide. No improvement. Toxic rash. *After admission:* Excision inner aspect. Incision outer aspect. Zinc peroxide. Skin graft
Case 2 J. G. 555,200 Adm. 8-15-38 Disch. 9-26-38 (Figs. 6 and 7)	Neck	Lymph node	4 mos.	35 das.	*Before admission:* Three children had ear infections. Patient developed sore throat and node on right side of neck. Ice bag, ultraviolet light, incision. Sulfanilamide. No improvement. Repeated incisions; ulceration; undermining. *After admission:* Excision. Zinc peroxide. Sulfanilamide intermittently because it upset digestion. Thiersch graft seventeenth day

BRIEF SYNOPSES OF THE 20 CASES TREATED (*Continued*)

CASES RECEIVING SULFANILAMIDE BEFORE ZINC PEROXIDE (*Continued*)

Name Hist. No.	Location	Type	Duration of Disease	Period of Treatment	Course
Case 3 H. O. 397,208 Adm. 9-6-38 Disch. 10-17-38	Penis and scrotum	Contam. Abrasion	2½ yrs.	40 das.	*Before admission:* Glans penis below meatus became red. Washes for 2 mos.—no effect Abscess incised. Cystostomy—open 13 mos. Bougies passed. Infection flared up. Ulceration under penis with undermining extending up over shaft and into scrotum. Sulfanilamide more than 1 mo.—no effect. *After admission:* Excision. Zinc peroxide. Skin graft
Case 4 N. F. 564,285 Adm. 10-31-38 Disch. 12-30-38	Axilla and arm	Lymph node	8 mos.	58 das.	*Before admission:* Nurse caring for hemo. strep. meningitis case. No known wound of hand. Developed node in left axilla. Incised. Kept on draining. Inoculated onto arm in 2 places. Opened and drained. Gradually became large ulcer with wide undermining. Ultraviolet, cod liver oil, sulfanilamide 3 wks. Toxic for W.B.C. Stopped. *After admission:* Excision ulcer. Lymphadenectomy. Skin graft
Case 5 E. N. 569,248 Adm. 12-26-38 Disch. 1-14-39	Leg	Contam. Mosquito bite	6 mos.	4 wks.	*Before admission:* Mosquito bite became infected. Incised and later excised. Sulfanilamide many weeks—no effect. Mercurochrome, carbolic acid, azochloramide, alcohol, balsam, brilliant red and strapping. All of no avail. *After admission:* Finally excised. Zinc peroxide. Oxyquinoline at the last
Case 6 H. H. 569,335 Adm. 12-30-38 Disch. 2-13-39 (Figs. 8, 9, 10, 11, 12, 13, 14 and 15)	Groin, thigh and leg	Lymph node	6 mos.	41 das.	*Before admission:* Took care of husband with sore throat. Developed sore throat herself and then swelling in right groin. Sulfanilamide by mouth and prontosil intramuscularly daily for 143 das.; mercurochrome, dichloramine T and saline locally. Scarlet fever antitoxin 5x, Welch antitoxin 2x. Transfusions 10x 1.0% prontylin dressings locally. Later alternating gentian violet and mercurochrome. Vaccine on 144th day. After sixth dose developed "erysipelas," which extended down to leg and foot, localizing there. Incisions. Increased doses of sulfanilamide. Blood level 11 mg. per cent. Started zinc peroxide; immediate improvement, but did not get adequate contact. *After admission:* Excised. Zinc peroxide. Skin graft tenth day
Case 7 R. W. Seen and and treated in private office only	Thigh	Lymph node	2 yrs.	4 wks.	*Before admission:* Splinter in foot. Abscess developed on inner side of left thigh. Incised. Continued to drain. Ulcer formed with moderate undermining and sinus formation. *After admission:* No excision. Adequate contact. Steady healing under ambulatory treatment

BRIEF SYNOPSES OF THE 20 CASES TREATED (*Continued*)

CASES RECEIVING SULFANILAMIDE BEFORE ZINC PEROXIDE (*Continued*)

Name Hist. No.	Location	Type	Duration of Disease	Period of Treatment	Course
Case 8 J. H. 561,802 Adm. 9-27-38 Disch. 4-1-39	Behind ears; both axillae; scrotum; perineum	Contam. Boils	Axillae; perineum and groins 6 yrs. Ears 8 mos.	145 das. in hospital	*Before admission:* For years had pimples and boils. Infection in groin spread down along scrotum to perineum. About same time, developed same lesion in axillae. 8 mos. ago he became inoculated behind both ears. Many hospitals, many opinions, many operations. Steady spread. *After admission:* Sulfanilamide. Improvement 2 wks., then standstill. Gentian violet. Cod liver oil. Repeated transfusions. Infection active again. Zinc peroxide. Immediate improvement. Needed more exposure. Too conservative
CASES RECEIVING SULFANILAMIDE WITH ZINC PEROXIDE					
Case 9 P. M. 499,980 Adm. 10-3-36 Disch. 12-9-36	Hip and thigh	Contam. T.B. sinuses	T. B. sinus 5½ yrs. Ulcer 16 mos.	10 wks.	*Before admission:* Limped as child of 3. Diagnosed by x-ray as tuberculosis of hip. Developed sinus in mid thigh and later one near hip. 10 mos. ago ulcer developed around sinus—gradually spreading extensively. *After admission:* Given sulfanilamide, and zinc peroxide, but after 1 wk. latter was stopped because could not get contact. Improved steadily with sulfanilamide. Grafted
Case 10 J. D. 548,884 Adm. 4-27-38 Disch. 5-21-38	Axilla	Lymph node	6 mos.	25 das.	*Before admission:* Little finger abraded at football Node became swollen in axilla. Opened and drained 4x. All kinds of antiseptics locally. Dakin's, mercurochrome, maggot fluid. Transfusions. Ulcer with overhanging skin flap. *After admission:* Zinz peroxide applied. Took sulfanilamide without discomfort. Rolled in margin cut away. Skin graft
Case 11 J. T. 531,057 Adm. 9-27-37 Disch. 10-24-37	Perineum and scrotum	Contam. Boils	26 yrs.	26 das.	*Before admission:* Began with a boil on the right buttock. Incision, prolonged drainage. Repeated operations. Never healed. Diagnosed T.B.; but no organisms found (Johns Hopkins Hosp.). Cribriform openings right groin. Sinus extending down along scrotum and up on other side. *After admission:* Excision. Zinc peroxide. Skin graft. Sulfanilamide taken—some nausea
Case 12 C. S. 446,461 Adm. 7-24-38 Disch. 10-6-38	Left axilla; perineum; abdom. wall	Contam. Boils	Axilla 12 yrs. Perineum and abdom. wall 5 yrs.	70 das.	*Before admission:* Has had pimples for years. Sores developed 8 yrs. ago in left axilla, undermined and formed an ulcer. 5 yrs. ago, infection began on lower abdomen and perineum. Diagnosed T.B. pig negative. Frei negative. *After admission:* Excision. Skin grafts. Sulfanilamide 14 das. Stopped because it upset digestion. Healing delayed by inability to stay quiet after skin grafts

BRIEF SYNOPSES OF THE 20 CASES TREATED (*Continued*)

CASES RECEIVING SULFANILAMIDE WITH ZINC PEROXIDE (*Continued*)

Name Hist. No.	Location	Type	Duration of Disease	Period of Treatment	Course
Case 13 D. K. 544,294 Adm. 2-21-38 Disch. 4-17-38	Thigh	Contam. Boil	17 mos.	53 das.	*Before admission:* Has had multiple pimples and boils for years. One took on new aspect with ulceration and undermining. Deep sinus formed. *After admission:* Excision. Zinc peroxide. Skin graft. Sulfanilamide started at time of operation and given for 19 das. Stopped because it upset digestion
Case 14 H. S. 511,367 Adm. 2-23-37 Disch. 4-8-37 (Figs. 16, 17, 18 and 19)	Axilla and chest	Lymph node	2 yrs.	41 das.	*Before admission:* Finger cut by manicure. Node swollen in axilla. Opened, drained. Ulcer developed with undermining beneath pectoral muscle, which became perforated in 2 places. Repeated operations; dakinization; anti-strept. vaccines; diathermy. Autogenous vaccine. *After admission:* Excision ulcer; pectoralis cut. Zinc peroxide. Sulfanilamide. High temp. and delirium 5 das. Fell abruptly on stopping sulfanilamide. Skin graft
Case 15 F. J. 535,644 Adm. 11-7-37 Disch. 12-21-37 (Figs. 20, 21, 22, 23 and 24)	Perineum and both axillae	Post-oper. hernia	19 yrs.	46 das.	*Before admission:* Operated upon for hernia in army in France. Wound became infected. Spread down along scrotum and up on other side. One year later, same infection in both axillae. Multiple operations. Diagnosed T.B. (Peter Bent Brigham Hosp.). Never proven. *After admission:* Excision. Zinc peroxide. Sulfanilamide. No temp. but delirium 4 das. Stopped on withdrawal of drug
Case 16 J. P. 558-089 Adm. 8-19-38 Disch. 9-30-38 (Fig. 25)	Leg	Contam. Pimple squeezed	14 mos.	38 das.	*Before admission:* Started when he squeezed a pimple on outer side of knee. Redness, swelling, abscess. Opened and drained. Did not heal. Undermining extended down onto leg. *After admission:* Excision. Zinc peroxide. Skin graft. Sulfanilamide. High temperature of 104° F. for 4 das. Stopped when drug was withdrawn

CASES RECEIVING SULFANILAMIDE AFTER ZINC PEROXIDE

Case 17 P. K. R.H. 366,011 Adm. 11-12-36 Disch. 3-4-37 (Figs. 26 and 27) Dr. W. C. White's patient	Hand and forearm	Contam. lacerated wound	5 mos.	16 wks.	*Before admission:* Cut back of hand with child's toy. Redness, swelling, pain, abscess. Incision, spread up to forearm. Incised. Formed ulcer with undermined margins. Treated with chlorazene, vaccines, phage. No improvement. Merck's zinc peroxide ineffective. *After admission:* Du Pont zinc peroxide—improvement but contact not adequate. Sulfanilamide added brought infection under control

BRIEF SYNOPSES OF THE 20 CASES TREATED (*Continued*)
CASES RECEIVING SULFANILAMIDE AFTER ZINC PEROXIDE (*Continued*)

Name Hist. No.	Location	Type	Duration of Disease	Period of Treatment	Course
Case 18 J. S. 489,587 Adm. 6-23-36 Disch. 10-28-36	Groin; abdom. and thigh	Lymph node	5 mos.	4 mos.	*Before admission:* Abraded toe. Node in groin. Incised, drained. Ulcer formed and spread up on abdomen and down thigh. Multiple incisions. Many antiseptics. Strep. serum injected around ulcer. Injection areas broke down. *After admission:* Excision and zinc peroxide. Femoral nodes involved. Removed piecemeal on several occasions. Femoral artery became involved; hemorrhage. Artery and vein partially excised. Skin graft. Prontosil given 4 das. with apparent spurt in wound healing. Stopped because it upset stomach
CASE RECEIVING SULFANILAMIDE ALONE					
Case 19 L. B. 501,444 Adm. 10-20-36 Disch. 12-24-36 (Figs. 28 and 29)	Breast	Contam. Pimple	9 mos.	20 wks.	*Before admission:* Began as a pimple near nipple. Abscess developed. Incised and drained. Continued discharge. Finally ulceration began and the whole breast became undermined. *After admission:* Sulfanilamide started with improvement in 6 das. Stopped with recurrence in 7 das. Started again and continued. No zinc peroxide. Plastic repair hastened healing
CASE RECEIVING ZINC PEROXIDE ALONE					
Case 20 W. A. 546,188 Adm. 4-6-38 Disch. 5-18-38 (Figs. 30, 31 and 32)	Perineum and buttocks	Contam. Boil	4 yrs.	40 das.	*Before admission:* Began as boil on side of anus. Incised. Kept draining. Gradually undermined all around anus and out on buttocks with multiple sinuses and cribriform openings. *After admission:* Excision. Zinc peroxide. Skin graft. No sulfanilamide

Technic of Treatment.—We believe that the ideal treatment of these cases is as follows: When the patient first comes to the hospital and after the diagnosis has been made by the clinical appearance of the lesion and confirmed by careful anaerobic as well as aerobic bacteriologic studies, zinc peroxide powder suspended in sterile distilled water in the consistency of 40 per cent cream, should be applied to the wound according to directions mentioned above, due care being taken to use effective material, to get contact and to prevent evaporation. This dressing should be removed daily. At the same time, sulfanilamide should be administered by mouth, 1.2 Gm. every four to six hours. If the patient tolerates the medication and there are no toxic symptoms, such as jaundice, destruction of red cells or white cells, high temperature or delirium, sulfanilamide should be continued. If toxic

symptoms supervene, it should be stopped. If after one week there are any areas of activity, one can be sure that an operative procedure is required to permit more adequate contact with the zinc peroxide. Such involved areas should be excised as far as can be done with safety to the life of the patient. Treatment should then continue as before. If there is any evidence of persistent activity after another week's time, further surgical attack should be instituted at once with a wider margin of excision.

It should be well understood that after surgical excision, for the first three or four days, the zinc peroxide is very adherent to the freshly cut surfaces, which have a gray, inert appearance, and it is difficult and unnecessary to wash off this adherent material. One is struck by the absence of inflammatory phenomena such as swelling or pain. Exposed nerves may be painful at first, and after the application of zinc peroxide, for a period of 15 minutes to an hour, there may be an uncomfortable burning sensation. If this occurs, it may be greatly ameliorated by flushing the wound surface with 2 per cent novocain before the reapplication of the zinc peroxide. On the fourth or fifth day, little areas of bright red granulation will appear and these will rapidly increase in size until the whole wound is covered. Then pain and sensitivity completely disappear. As soon as new epithelium grows in from the margin, we are assured that skin grafts will take. In most instances, the small deep grafts are most suitable and there should be almost 100 per cent success. The grafts should be held in place by a single layer of coarse meshed gauze sealed at the skin margin with collodion. They should then be covered with fine meshed gauze wet with saline and cut to the pattern of the wound and then with wet saline compresses and sealed with vaseline or zinc oxide ointment for 24 hours. The following day, the zinc peroxide suspension should be applied over the coarse meshed gauze, gauze compresses or sheet cotton, wet with distilled water, added and the dressing sealed as before. In another 24 hours, the coarse meshed gauze may be removed and the zinc peroxide applied directly to the grafts. All living grafts will be well attached and pink by that time.

As soon as new epithelium begins to grow out from the margins of the grafts, if cultures fail to reveal any viable hemolytic streptococci on anaerobic culture, it is well to change over to 0.5 per cent oxyquinoline in 5 per cent scarlet red ointment which seems to stimulate the rapid growth of epithelium and hasten the final closure of the wound.

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DISCUSSION.—DR. WM. BARCLAY PARSONS (New York, N. Y.): Doctor Meleney is to be congratulated for adding another chapter to his brilliant work on this very important type of infection. Doctor Cutler's remarks on surgical training and surgical possibilities, *etc.*, are well exemplified in Doctor Meleney's work. He has been interested in the symbiosis of organisms and its effect. The "symbiosis" of a careful, well-trained surgeon and the bacteriologic laboratory, also, has its very definite effect.

We have heard so many enthusiastic reports on the use of sulfanilamide that one can perhaps be pardoned if one takes a little pleasure in hearing a report not too enthusiastic about the use of sulfanilamide; and yet that is not so trivial a point of view as it may seem, because here, there is an attack based upon a very definite set of circumstances, and it is perhaps reasonable, as Doctor Meleney pointed out, that sulfanilamide should not have such a striking success in a chronic, thick-walled, fibrotic, dense area as it would in a fresh, new infection where the drug can be delivered to the organisms.

He did not emphasize, as perhaps he might have, although he has emphasized it, I think, in other communications, just that exact point, namely, the delivery of the agent to the organism and the preparation of the wound so that the agent can be delivered to the organism.

The first point that he has mentioned as essential to success in this type of treatment, namely, an effective material, is reasonably obvious, and he has mentioned in other papers the difficulties that he has had at times, and which others have likewise had, with an imperfect material.

Secondly, the question of absolute contact of the material depends so essentially on the adequate preparation of the wound. It is much like the Carrel-Dakin treatment during the war; a good many people said: "Oh, that is no good at all," and then it was reasonably obvious that those individuals were not preparing their wounds for the use of the Dakin solution as they should have. That is so essential in these wounds, certain examples of which

he has demonstrated. Control of evaporation, of course, is important so that the material can continue to act.

A fourth, and certainly equally important, element is the dressing of these cases. Doctor Meleney has never suggested, I think, although I suspect him of feeling it, that the reason for the delay in some of these cases that were handled for weeks and months elsewhere and then came to him and were cleaned up, was the fact that they had not been carefully and properly and thoroughly handled. When he dresses one of these cases, the whole thing is just as though it were a major operation—gowns, gloves, and all the technic that we consider essential to a major operative procedure, and the dressings are done with the most meticulous care. It is advisable during the whole course of the case that these dressings should be done by one man, or at most by two, who are in daily attendance upon that particular patient.

This is a very interesting contribution, and I think it is of real interest that the original scheme which he devised really is the successful one, and that only in a few of the cases does the sulfanilamide act as a helpful adjuvant.

Dr. Robert I. Harris (Toronto, Canada): The importance of Doctor Meleney's contribution this morning and those of previous occasions cannot be overestimated. While this condition is rare, the magnitude of the surgical problems it presents is so great that only the principles which Doctor Meleney has laid down have provided us with any means of handling the otherwise insuperable difficulties. Adequate exposure of the wound, the use of an agent which will provide an atmosphere of high oxygen tension over an adequate period of time, and now the use of sulfanilamide are the essential points in treatment.

Doctor Meleney has pointed out that the use of sulfanilamide produces marked improvement, sometimes brilliant results, but that it is not free of difficulties, especially because of its toxicity. It is in this connection that I wish to call to the attention of Doctor Meleney and the fellows of this Association that the concomitant administration of nicotinic acid, in doses of 50 mg. four times a day, reduces the toxic symptoms of sulfanilamide very greatly and frequently eliminates them. In an exceptionally difficult problem of this type which I have had to handle recently, the use of nicotinic acid transformed our problem. This is an empiric use of nicotinic acid for which I am indebted to my medical colleague, Dr. Hurst Brown.

Dr. Herman E. Pearse (Rochester, N. Y.): I do not think it is surprising that sulfanilamide does not increase the action of zinc peroxide, for zinc peroxide is so efficacious in and of itself. One complication that we have had in the use of this agent is not from the drug itself, but in the preparation of the wound. We have one instance of dissemination of infection with generalized sepsis and metastatic abscess. Under these circumstances, with dissemination of infection, sulfanilamide might be of value. I hope it will not be a digression to mention another use of zinc peroxide: Recently, we had a case of Welch bacillus infection in an open wound which could not be cleared up and the wound could not be healed. Roentgenotherapy, sulfanilamide, and many other local measures were tried. It was then treated with zinc peroxide, which resulted in a rapid subsidence of the infection.

Dr. Frank L. Meleny (closing): Doctor Pearse's success with the use of zinc peroxide in a Welch bacillus infection has been very gratifying to hear. The clinical effectiveness of zinc peroxide was first observed in cases

of undermining ulcer where we were dealing with an organism, which is micro-aerophilic, that is to say, intermediate between the aerobes and the anaerobes. Naturally, therefore, we applied it at once to the whole series of surgical anaerobic bacteria. In the near future, in the ANNALS OF SURGERY, there will appear a paper which gives our laboratory, and, to some extent, our clinical experiences with anaerobic infections and with the organisms producing them.[4]

The scattering of organisms into the blood stream at the time of operation must be borne in mind, and excessive manipulation of the tissues must be avoided. This complication must be very rare, however, because it occurred in only one of 40 cases which we have seen. This case was included in the second paper of this series. At autopsy, it was found that the patient had a suppurative thrombophlebitis of the common iliac vein.

I am particularly interested to hear of Doctor Harris' experiences with nicotinic acid, and we will certainly take the first opportunity to apply that experience to cases that come to us which show toxicity from sulfanilamide.

Just two other things I would like to add. One is that there is in the literature and perhaps in the minds of some of you, a confusion between two distinct clinical entities exhibiting chronic ulceration. The chronic, undermining, burrowing infection, which I have described and illustrated in the present paper, is characterized by extensive undermining of the skin and burrowing into the deep tissues but without any gangrene. We believe that it is not a symbiotic infection, but caused simply and solely by the micro-aerophilic *hemolytic* streptococcus. Then, there is the symbiotic, progressive gangrenous ulcer, in which there is always gangrene of at least a part of the margin with no undermining of the skin and no deep penetration. If the infection arises from a deep abscess, for example, a pleural or peritoneal abscess, the deep pocket closes and the gangrenous ulcerative process goes on in the skin and subcutaneous tissues in only a very superficial manner, destroying tissue massively as it goes. In that infection, there is another micro-aerophilic organism which is *nonhemolytic* and which can be found out in the periphery in pure culture, and it is always combined with a staphylococcus in the zone of gangrene. It is, therefore, called a symbiotic or synergistic infection.

The second point is that I would like to make a plea (and I do so at every opportunity) that members of surgical departments, particularly the chairmen of those departments and the directors of surgical services, should insist upon more adequate anaerobic bacteriology in their hospitals and on their services.

FAT EMBOLISM *

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FAT EMBOLISM occurs somewhat infrequently as a complication of fractures and of operations upon bone. Its recognition is not easy, and almost certainly, many cases, even though they end fatally, are not recognized in their true nature. There are two reasons for this difficulty. First, in fatal cases which come to postmortem, the presence of fat emboli will not be detected unless the sections are prepared by special methods. Preparation of paraffin sections for hematoxylin and eosin stains involves dehydration in graded alcohols, and this dissolves out the fat globules. These can be demonstrated only by fat stains in frozen sections. Second, in those cases which do not end fatally, the clinical picture is not clearly defined or easily recognized. As yet, we lack a definite and certain clinical method or sign whereby the underlying pathologic cause can be recognized. At the moment, the strongest clinical evidence of the presence of fat embolism is presented by a certain rather characteristic sequence of events through which most cases pass. The sequence is as follows: (1) An injury to a bone or an operation upon a bone. (2) An interval in which the only symptoms and signs the patient presents are those related to his fractured bone; followed by (3) a period in which there develop (a) pulmonary signs and symptoms, and (b) cerebral signs and symptoms. This is followed by death or recovery. Occasionally, though rarely, fat globules may be recovered in the sputum or in the urine. These are signs of great diagnostic value but unfortunately they are rarely present, and their absence does not by any means rule out fat embolism. Similarly fat emboli in cutaneous capillaries may manifest their presence by the appearance of petechial hemorrhages in the skin. This also is a rare finding but of great value when it is present. Its absence also does not rule out the presence of fat embolism.

Because of this confusion and difficulty in clinical diagnosis, the report of a fatal case, which presented a clinical sign heretofore unrecognized, seems of value.

Case 1.—*Fatal case of fat embolism complicating fracture of the femur. Profound fall in hemoglobin due to hemorrhagic exudate into lungs as a reaction to pulmonary fat embolism.*

S. G., male, age 22, was admitted to the hospital, July 4, 1936, with a transverse fracture of the left femur, sustained when he was knocked down by a motor car. He was conscious and not in shock. The only injury he had sustained was the fracture of the femur. Roentgenograms showed it to be a transverse fracture of the middle third of the

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left femur with overlapping of the fragments and three-quarters of an inch of shortening. Temperature 98.6° F., pulse 108.

Ten hours later, a Kirschner wire was passed through the lower fragment and traction applied. During the day his temperature rose to 101° F. and his pulse to 120, but he was comfortable and made no complaints.

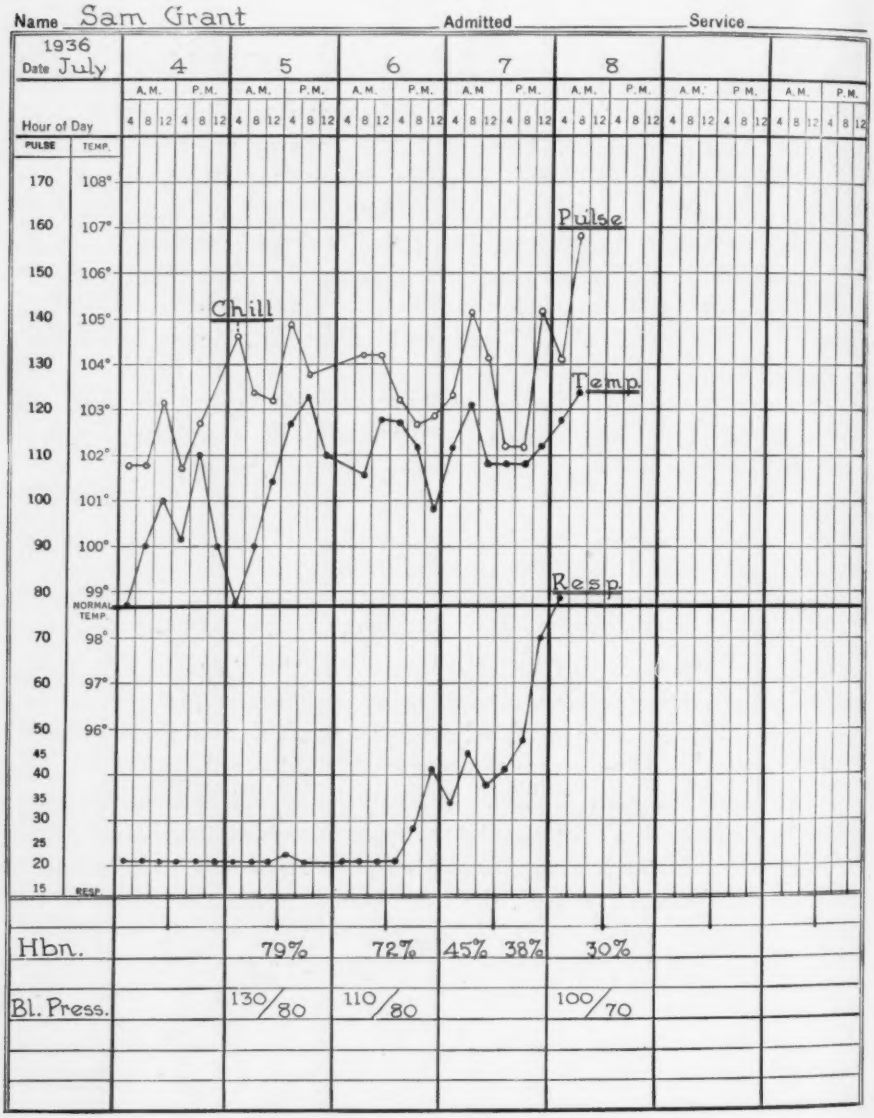


CHART 1.—The clinical chart of Case 1; pulse, temperature and respirations with records of the hemoglobin estimation and blood pressure.

On July 5, he had a chill, after which his temperature rose to 103° F. and his pulse to 140. Examination showed him to be very restless, sweating and pale. So marked was the pallor that a serious internal hemorrhage was suspected. However, no evidence of this was found on examination, nor was there a large hematoma at the site of fracture.

The hemoglobin was 79 per cent. Chest examination showed impairment of air entry at the right base and a few râles. Blood pressure 130/80.

On July 6, two days after admission, a radical change had occurred. The patient was very ill, pale and irrational; pulse 130, temperature 102° F., respiration 30, hemoglobin 72 per cent, R.B.C. 4,000,000. Complete examination revealed no findings which seemed adequate to account for this profound change. The chest findings were as previ-

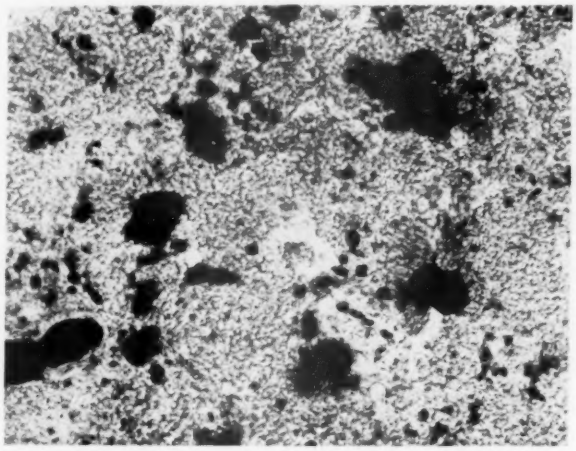


FIG. 1.—Case 1: Photomicrograph of the lung, showing extensive fat embolism and the alveoli filled with hemorrhagic exudate. Stained with scharlach R. (×160)

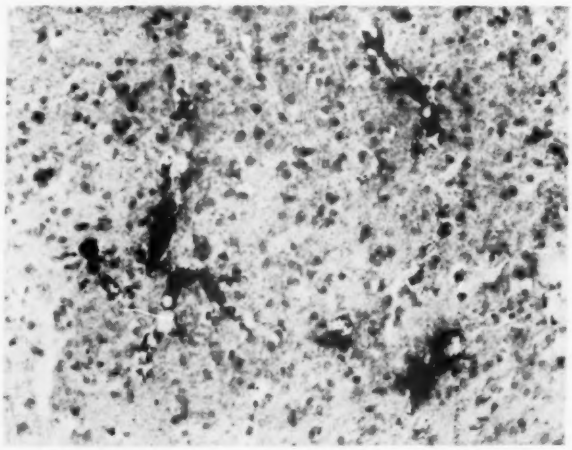


FIG. 2.—Case 1: Photomicrograph of the brain showing numerous fat emboli in the cerebral capillaries. Stained with scharlach R. (×160)

ously noted but slightly more marked. Roentgenograms of the chest excluded the presence of blood or other fluid in the pleural cavity. During the day he became increasingly dyspneic and the respiratory rate reached 40. He presented the appearance of shock or hemorrhage and gradually became stuporous and irrational. Reestimation of the hemoglobin showed it to be 72 per cent. The blood pressure was well maintained at 110/80, in spite of the appearance of shock.

On July 7, the clinical picture was similar but accentuated, pulse 140, temperature 103° F., respiration 50. He was pale, irrational and stuporous and at times violently restless. Chest examination revealed, for the first time, consolidation involving the right lung and beginning in the left lung. Hemoglobin had dropped to 45 per cent and in the evening was 38 per cent. For the first time, cough was present and once he brought up blood-tinged sputum. Unfortunately this sputum, the only sample he coughed up during his illness, through a misunderstanding was not examined for fat. The urine contained albumen but did not contain fat droplets. There were no petechial hemorrhages in the skin.

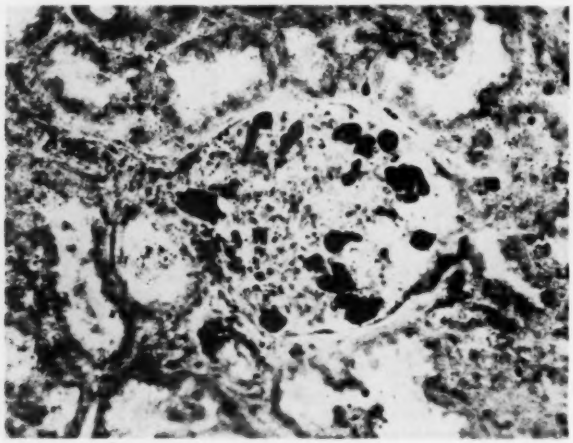


FIG. 3.—Case 1: Photomicrograph of kidney showing fat emboli in a glomerulus. Stained with scharlach R. (×160)

The patient died the following noon, four and one-half days after his injury. Before death the pulse was 140, temperature 103° F., respiration 70, and hemoglobin 30 per cent. Blood pressure 100/70 (Chart 1). Signs of consolidation were present over the whole of the right lung and all but the apex of the left lung. On these findings a diagnosis of death from pneumonia complicating fracture was made by our medical colleagues, though past experience with fat embolism made us suspect this as the cause of death.

Pathologic Examination.—Gross: Lungs—Both pleural cavities were free of fluid and adhesions. Both lungs were solid and did not crepitate except for a small area in the apex of the left lung. The consolidated lungs were dark red in color, resembling liver in appearance. (Note that this could well be regarded as the picture of pneumonia in the stage of red hepatization.) Large quantities of bloody fluid could be expressed from the cut surfaces. The pulmonary vessels were free from thrombus.

Brain.—The cut surface showed numerous scattered small areas of petechial hemorrhage.

Left Femur.—Showed a transverse fracture with a hematoma of moderate size.

The microscopic findings were of the greatest interest and importance.

Microscopic: Lungs (Fig. 1).—The alveoli were completely filled with a hemorrhagic exudate consisting almost entirely of red blood cells and fluid. Unlike the picture of pneumonia, leukocytes were few in number. Stained with scharlach R., the lung capillaries were found to contain numerous globules of fat of all sizes. The picture was that of an intense hemorrhagic exudate filling the alveoli, with numerous fat emboli in the capillaries. Inflammatory cells were very few in number.

Brain (Fig. 2).—Stained with scharlach R., many capillaries were seen filled with fat globules, each surrounded by a zone of necrosis.

Kidney (Fig. 3).—Fat stains showed numerous globules of fat in the capillaries of the glomeruli.

Liver.—A few fat emboli were found here also.

SUMMARY AND COMMENT.—The significant findings in this case of fatal fat embolism were as follows: The course of events, broadly considered, was that of most cases of fatal fat embolism, namely, (1) a serious injury to a bone followed by (2) an interval in which the only signs and symptoms were those related to the injured bone. Then came (3) the onset of serious pulmonary and cerebral signs and symptoms, progressing to death. It is noteworthy that from clinical signs and gross postmortem evidence the pulmonary lesion might well have been regarded as pneumonia. Only the sections stained with scharlach R revealed the true pathology to be pulmonary fat embolism with hemorrhagic exudate into the alveoli.

The unusual feature of this case, or at any rate the feature which heretofore has not been recognized as an accompaniment of fat embolism, was the profound fall in the red blood cell count and hemoglobin content of the blood. So great, and so evident, was this anemia that a concealed hemorrhage was suspected. The great fall in the red blood cell count of the blood is adequately explained by the postmortem findings in the lungs. The pulmonary consolidation was due to an exudate into the alveoli which consisted almost exclusively of erythrocytes and serum. The enormous amount of this exudate would adequately account for the great and sudden fall in erythrocytes and hemoglobin in the circulating blood. We shall attempt to discuss the mechanism of its production later.

For some time prior to the occurrence of this fatal case of fat embolism, our attention had been drawn to the severe and progressive fall in erythrocyte count and hemoglobin percentage which occurred in certain patients following bone operations, notably spinal fusion and arthrodesis of the hip. It did not seem that this could be accounted for by loss of blood at the time of operation, first, because it was much greater than the blood loss and, second, because it was progressive over a relatively long period of time. Table I

TABLE I

ILLUSTRATING THE PROGRESSIVE AND MARKED FALL IN ERYTHROCYTES AND HEMOGLOBIN FOLLOWING OPERATIONS UPON BONE. UNEXPLAINED BY PRIMARY BLOOD LOSS

Case		Hemoglobin	Red Blood Count
J. D.:	October 11, 1933	98%	4,750,000
	October 12, 1933	Arthrodesis of Hip	
	October 19, 1933	60%	3,000,000
	October 31, 1933	45%	2,750,000
	November 28, 1933	83%	4,750,000
J. B.:	July 23, 1935	110%	5,400,000
	August 8, 1935	Spinal Bone Graft	
	August 10, 1935	85%	4,328,000
	August 23, 1935	74%	3,616,000
	September 5, 1935	95%	4,800,000

illustrates two such examples. It is just possible that the progressive loss of red blood cells in these cases can be accounted for by pulmonary fat embolism and the accompanying hemorrhagic exudate. At any rate, the following case seems, clearly, to be a case of pulmonary fat embolism following operation, analogous to the fatal case just described.

Case 2.—*Probable pulmonary fat embolism following spinal fusion for scoliosis; marked pulmonary signs and symptoms; marked cerebral symptoms and profound fall in hemoglobin. Recovery.*

A. E. R., female, age 20, was operated upon, October 22, 1936. A spinal fusion for scoliosis was performed, extending from the fifth to the twelfth dorsal spine, inclusive. Large grafts taken from the tibia were employed for this purpose. The operation was expeditiously performed and she suffered no shock. A transfusion of 500 cc. of blood was administered. For two days following operation she vomited repeatedly but otherwise seemed in satisfactory condition. On the fourth day, there suddenly developed some type of pulmonary catastrophe, characterized by cyanosis, fever (101° F.), rapid pulse (130), and increased respirations. Adequate examination of the chest was impossible because she was encased in plaster. On the fifth day, she seemed moribund. On the sixth day, delirium developed and continued for three days, notwithstanding the fact that the respiratory symptoms were improving. From the tenth day on she made steady and rapid improvement and ultimately made a complete recovery.

The acute and serious complication she passed through was accompanied by a profound fall in hemoglobin. The first record we have was 45 per cent, taken on the day of the onset of the pulmonary symptoms, and this in spite of the transfusion which had been administered following operation. Two days later it was 40 per cent; the next day 34 per cent, and following a transfusion rose to 45 per cent. On the succeeding days the estimations were 50, 62, 70 and, finally, on November 10, 81 per cent following another transfusion.

COMMENT.—This, then, is a patient who, following an extensive operation upon bone, developed a serious complication manifested by cyanosis, respiratory distress, fever, tachycardia, increased respiratory rate, delirium, semicoma and, finally, a rapid and extreme fall in hemoglobin content. The similarity to the preceding case of proven fat embolism, which was fatal, is so great that one must consider fat embolism as a probable cause of her symptoms also.

Incidence of Fat Embolism.—The occurrence of fat embolism is rare but there is reason to think that it is more common than is supposed. The difficulty of recognizing the condition, both clinically and at postmortem, undoubtedly results in many cases being overlooked. Our interest in this condition was stimulated, four years ago, as the result of a postoperative death from fat embolism, proven at postmortem. The operation was an arthrodesis of a tuberculous hip. Prior to that date the diagnosis of fat embolism does not occur in the records of the Toronto General Hospital. Since then we have been able to recognize six fatal cases and in addition six nonfatal cases in which the diagnosis of fat embolism is almost certain, though without the confirmation of sections, some doubt must always exist as to the accuracy of this diagnosis. It would seem that fat embolism, even though rare, is more common than is supposed; that it is easily overlooked; and that a consciousness of its possible existence may lead to its more frequent recognition.

BRIEF CLINICAL RECORDS OF FATAL CASES OF FAT EMBOLISM

Case 1.—Reported herewith.

Case 2.—This case has been reported previously[2] (J.A.M.A., **195**, 1013, September 28, 1935). A boy, age 17, suffering from tuberculosis of the hip, was operated upon for the purpose of fusing his diseased hip. Transfusion of 500 cc. of blood followed his operation, which presented no difficulties. Six hours after operation he became cyanosed and dyspneic, and complained of a sense of constriction about the chest. Cyanosis increased, pulse became rapid and feeble, and temperature rose to 103° F. He died 20 hours after operation. Postmortem examination revealed extensive fat embolism of lung.

Case 3.—A man, age 39, sustained a fractured femur in a motor accident. This limb had previously been injured at the knee in such a manner as to necessitate the use of a plaster encasement for a prolonged period of time. It is possible that the bone atrophy from disuse may have been a factor which facilitated the production of fat embolism. Six hours after his accident he became unconscious and died 54 hours later without regaining consciousness. Postmortem revealed extensive fat embolism of lungs and brain. (Courtesy of Dr. J. L. McDonald.)

Case 4.—A woman, age 73, sustained a fracture of the neck of the femur, May 12, 1934. It was reduced and fixed with a Smith-Petersen nail, May 17, 1934. For a few days following operation, she presented no untoward symptoms except a continuous fever. She then developed respiratory symptoms and signs, followed by delirium and coma. Death occurred ten days after operation. Postmortem examination revealed consolidation of the lung bases and, on section, fat emboli in the pulmonary capillaries. The brain was not examined.

Case 5.—A man, age 50, sustained a fracture of the tibia and fibula, November 28, 1935. It was reduced under local anesthesia on the day of admission. On the second day he was stuporous and hard to rouse. There was no evidence of head injury and neurologic examination was negative. Coma deepened and râles and bronchial breathing were found in both lungs. No fat was found in urine or sputum. He died in coma six days after the accident. Postmortem showed consolidation of both lung bases and numerous petechial hemorrhages in brain. Fat embolism was demonstrated on section of lungs and brain.

Case 6.—A woman, age 32, was operated upon, February 17, 1937, for stabilization of the hip. The operation was extensive but no great difficulty was encountered. Postoperative course was complicated primarily by distention and vomiting. On the second postoperative day she became cyanosed and dyspneic. The distention was controlled on the third postoperative day but the cyanosis and respiratory distress increased. Coma developed toward the end of this day and rapidly deepened until death. One hemoglobin estimation, made on the day of her death, was 47 per cent. Postmortem was not permitted. In the absence of definite postmortem evidence the diagnosis of fat embolism is, of course, presumptive, but from the course it seems reasonably certain that this was the cause of death.

NONFATAL CASES

Probable Diagnosis, Fat Embolism

Case 1.—Reported herewith.

Case 2.—This case has been reported previously[2] (J.A.M.A., **195**, 1013, September 28, 1935). A man, age 35, sustained a fracture of the tibia, April 2, 1935. The fracture was reduced, April 2, 1935. He remained conscious and mentally clear until April 5. On April 6 he became restless and uncooperative. He was dull and semicomatose. Temperature 102° F., pulse 180. Coughed up bloody sputum. He remained comatose and irrational until April 12, when he began to improve. By April 19, he had completely recovered from the cerebral lesion. Urine collected, April 7, contained fat. On April 16, he developed a patch of pleurisy on the right side which cleared up within two days and,

on April 23, a similar transient pleurisy occurred on the left side. The sputum was not examined for fat. (Courtesy of Dr. K. G. McKenzie.)

Case 3.—A man, age 31, sustained a fracture of the femur, August 17, 1938. Twenty-four hours later he became drowsy and stuperous and slowly became unconscious. Examination showed no sign of injury to head; cranial nerves normal. No paralysis of legs. There were numerous petechial hemorrhages in skin of trunk and neck. Lumbar puncture showed a pressure of 250 Mm. without increased protein or cells. Bur holes in either temporal fossa showed absence of hemorrhage and the presence of a large collection of spinal fluid under tension in the subarachnoid space. Recovery followed. (Courtesy of Dr. E. H. Botterell.)

Case 4.—A man, age 30, sustained a fracture of the tibia. Thirty-six hours after his injury he became restless and irrational. Respirations were increased and he was cyanosed. Unconsciousness developed. The lung bases showed dulness and râles. Sputum and urine contained fat globules. After a stormy convalescence, during which there were extensive signs in both lungs, he recovered completely. (Courtesy of Dr. Wm. S. Keith.)

Case 5.—A man, age 19, sustained a fracture of the femur, August 6, 1938. He presented no symptoms other than those associated with his fractured femur until August 12, on which day the fracture was manipulated in an effort to secure reduction. He collapsed on the table, pulse became rapid and feeble and the blood pressure fell. This was followed by pulmonary signs and mental confusion, persisting for about two days. Hemoglobin estimation at that time was 50 per cent. He ultimately made a complete recovery. (Courtesy of Dr. S. Gordon.)

Case 6.—A man, age 35, sustained fractures of the forearm and leg and was admitted in shock, October 21, 1935. Was rational on October 22. On October 23, he became comatose with stertorous breathing of intermittent rhythm. He slowly became cyanosed and dyspneic and deeply unconscious. On October 25 he had improved, though expectorating bloody mucus; and from then on he slowly recovered. He had no head injury. (Courtesy of Dr. Gordon Cock.)

Experimental Data.—The fatal case we have recorded presents two problems which demand explanation: (1) How could a relatively small amount of fat cause such a severe reaction with a fatal ending? The injury to the femur was not extensive and the resulting hematoma was only of moderate size. The amount of fat available from this fracture could not have been more than a small fraction of the total amount in the medullary space of the femur and this of itself is not very great in amount. (2) How could such a bland body constituent as fat cause such an intense irritative reaction of a hemorrhagic nature? We have attempted to find an answer to these problems by the experimental investigation recorded below. Though we have not succeeded in reproducing the profound fall in hemoglobin, we have succeeded in reproducing the lung changes including the hemorrhagic exudate.

Protocols of Experiments Using Neutral Human Fat.—Rabbits of approximately the same size (2 Kg.) were used throughout these experiments. Human fat obtained at operations in which bone grafts were removed from the tibia was the material utilized to cause the fat embolism. Most workers in experimental fat embolism have used vegetable or mineral oils. It seems quite possible that this does not reproduce exactly the conditions which exist in human cases. For that reason human fat was used. It is easily obtained in amounts from 10 to 20 cc. from the medullary cavity of the tibia when a graft has been removed. As it is quite fluid, it can be aspirated from the bed

of the graft with a syringe. The fat was separated from the small amount of blood present by incubating the material at body temperature and subsequently decanting the clear supernatant fat.

Using such material we were able to establish that the minimum lethal dose for rabbits is 0.9 cc. of neutral human fat per kilo of body weight given in one dose. Attempts were then made to cause a fall in hemoglobin by repeated sublethal doses administered over a period of time. Repeated injections of neutral human fat in doses up to 0.5 cc. per kilo reaching in some cases a total of 15 cc. of fat per animal (approximately 7.5 cc. per kilo) could be given without causing death, though marked pulmonary symptoms (dyspnea) and cerebral signs (ataxia and incoordination) were produced. Note that the minimum lethal dose for a single administration is small—

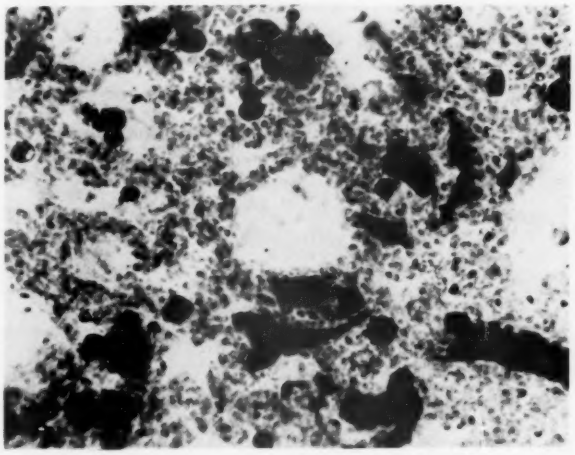
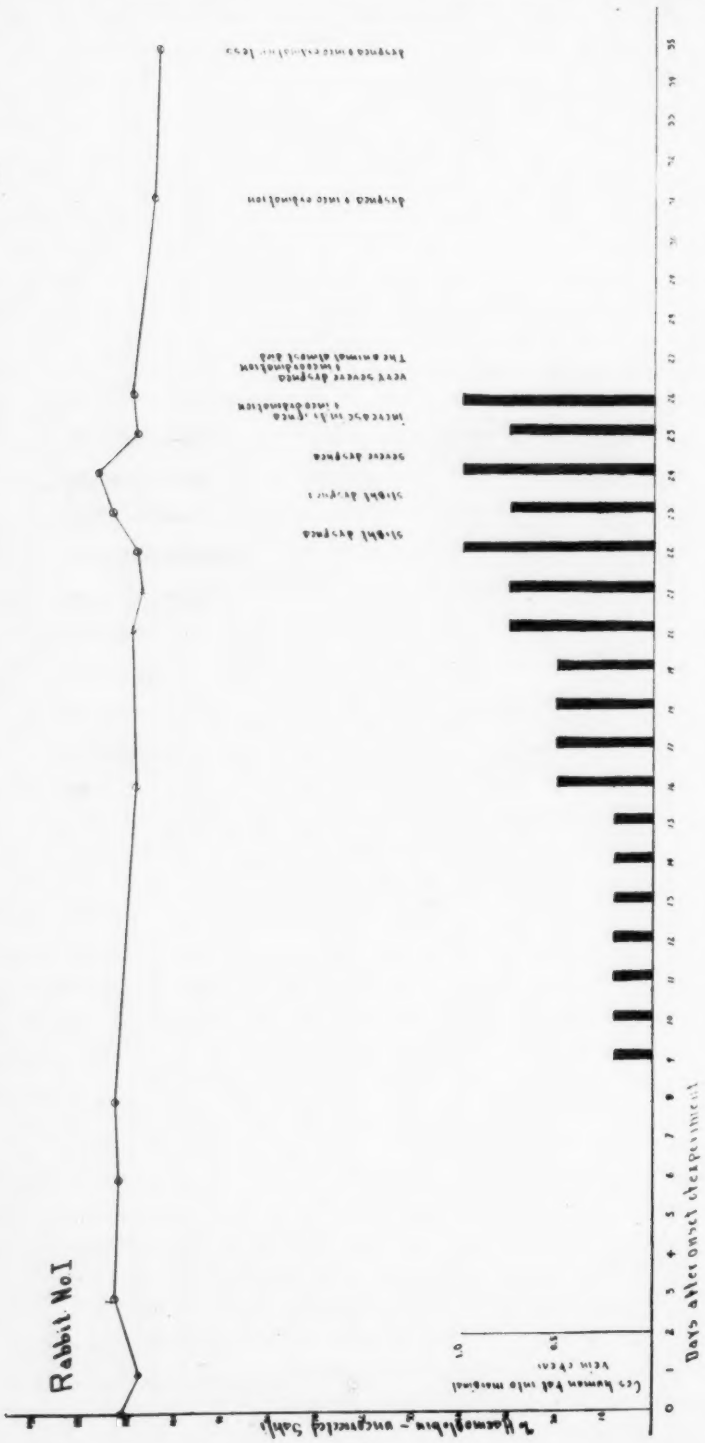


FIG. 4.—Photomicrograph of lung of rabbit following repeated injection of sublethal doses of neutral human fat. Very numerous fat emboli. Frozen section; scharlach R. (×160)

0.9 cc. per kilo. This would be the equivalent of 63 cc. for a 70 kilo (150 pound) man. Note also that when half the minimum lethal dose is given repeatedly, relatively enormous amounts of fat can be administered. At postmortem these animals showed stiff, solid lungs which looked and felt like liver, with numerous fat emboli in lungs, liver, kidney and brain (Fig. 4). The pulmonary alveoli were filled with a hemorrhagic exudate of moderate intensity. There was no significant fall in hemoglobin (Chart 2).

Protocols of Experiments Using Hydrolyzed Human Fat.—The intensity and the hemorrhagic nature of the reaction in the lung and also in the brain and the skin suggest that some change may have occurred in the fat which renders it an irritating rather than a bland body fluid such as one might naturally consider it to be. We are indebted to Professor W. K. Franks, of the Department of Banting Medical Research, for the suggestion that perhaps these intensely irritating qualities are the result of splitting of the neutral fats into glycerol and fatty acids by tissue lipases; either at the site of the injury to the bone or in the lung. With this in mind another set of experiments was


Rabbit No I
Days after onset of experiment
Vein effect
Leg

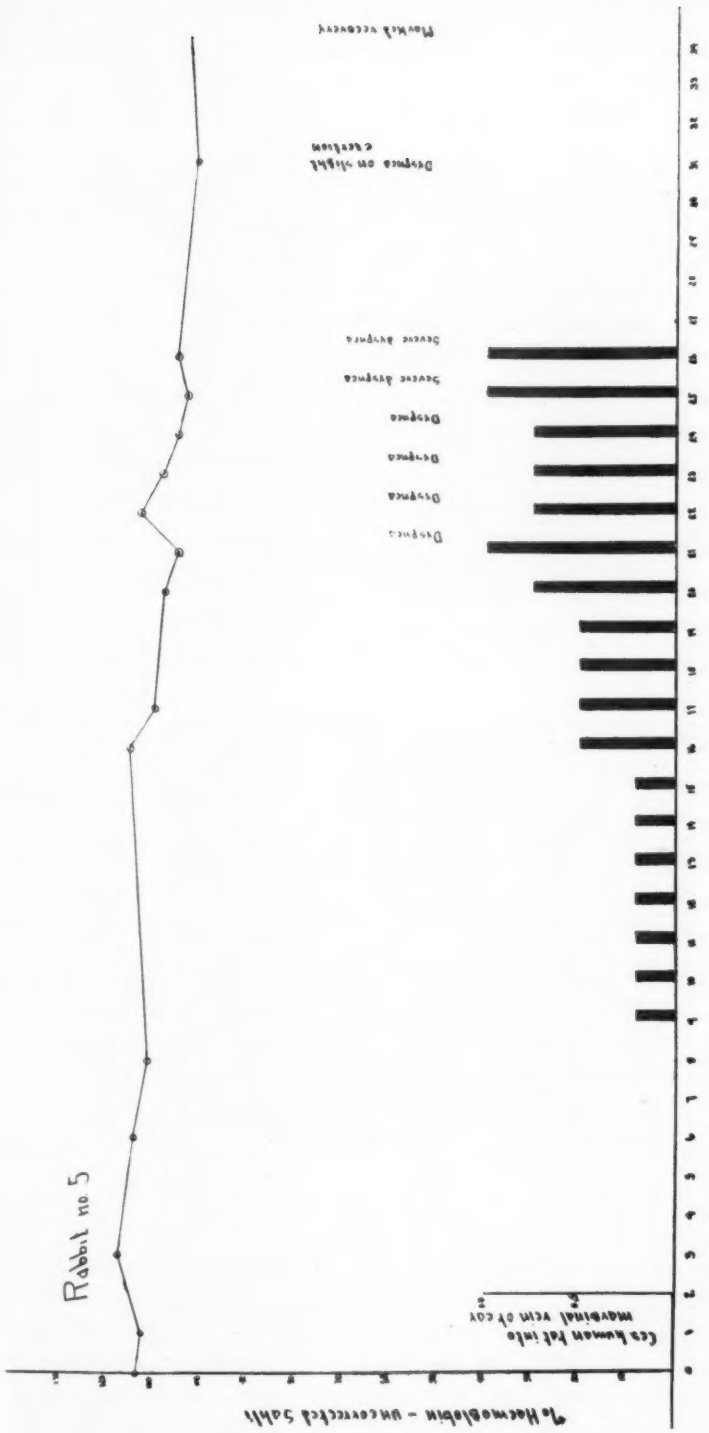


CHART 2.—Graphs of two experiments on the production of fat embolism in rabbits following repeated sublethal doses of neutral human fat.

undertaken, also upon rabbits, in which human fat hydrolyzed with dilute hydrochloric acid was used. The excess of acid was neutralized by an alkali before injection.

These experiments showed that the minimum lethal dose of hydrolyzed

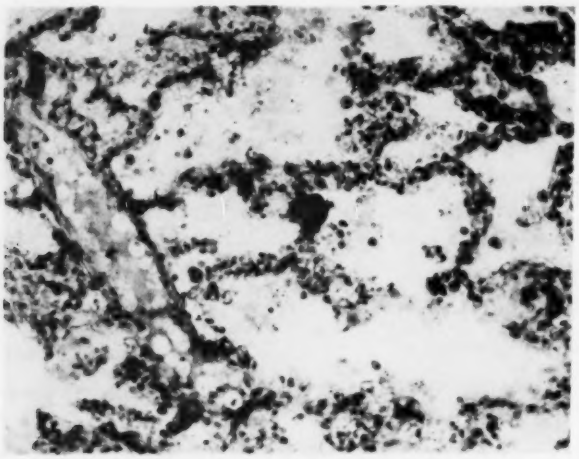


FIG. 5.—Photomicrograph of lung of rabbit following repeated injection of sublethal doses of hydrolyzed human fat. Few and small fat emboli. Frozen section; scharlach R. (×150)

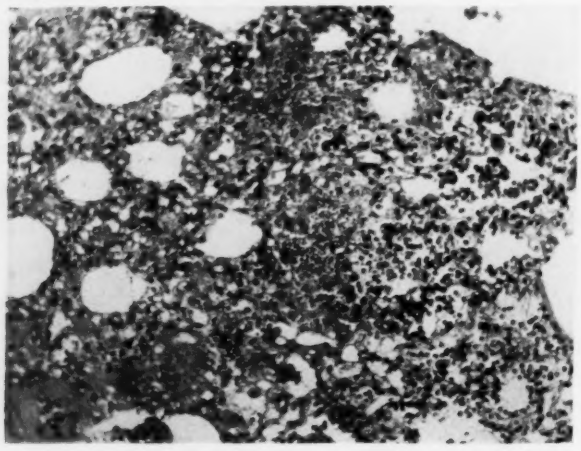


FIG. 6.—Photomicrograph of same rabbit's lung as Figure 5. Illustrating the hemorrhagic and serous exudate in the pulmonary alveoli similar to that seen in the fatal human case. H and E stain. (×150)

fat was 0.07 cc. per kilo of body weight, *i.e.*, less than one-twelfth the minimum lethal dose of the neutral fat. Repeated injections with 0.035 cc. per kilo (one-half the minimum lethal dose) were all fatal in five doses. The hydrolyzed fat, therefore, is very much more toxic in single doses than neutral fat, and repeated injections of small doses are tolerated much less well. Postmortem examination showed only a few fat emboli in the lungs

but the alveoli were filled with a hemorrhagic exudate closely resembling that seen in the fatal human case recorded (Figs. 5 and 6). No significant change in hemoglobin content of the blood was observed (Chart 3).

COMMENT.—These experiments demonstrate certain facts of importance. The administration of a comparatively small amount of fat in the single dose is rapidly fatal. If the fat is administered in small repeated doses over a

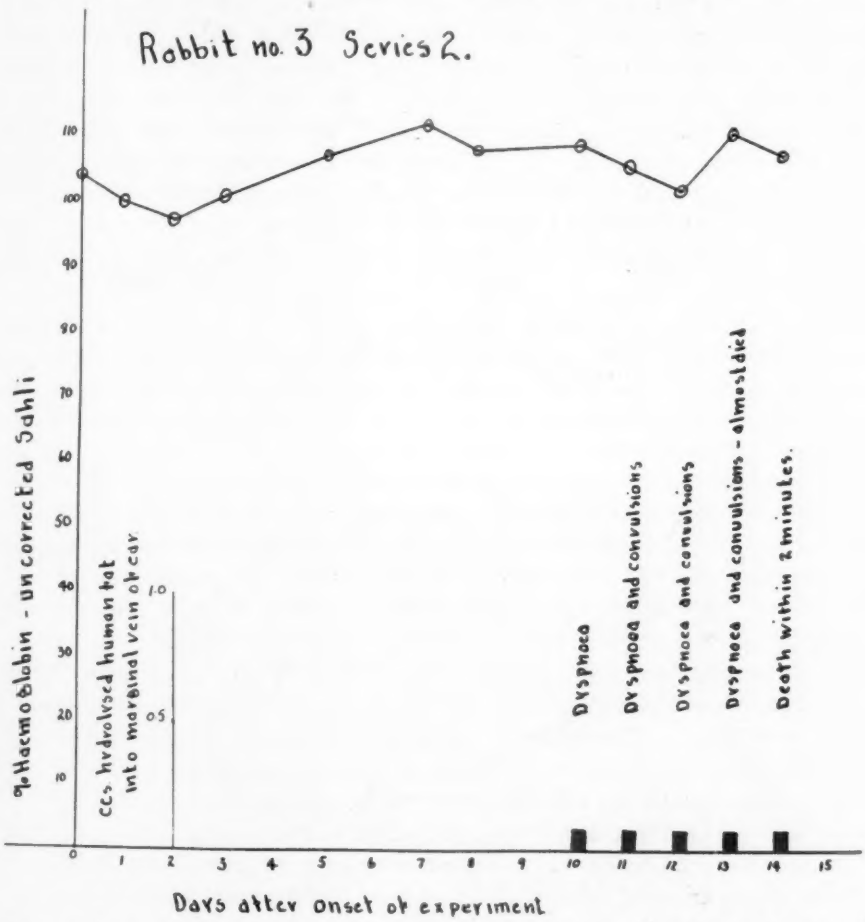


CHART 3.—Graph of an experiment on the production of fat embolism in a rabbit following the repeated injection of sublethal doses of hydrolyzed human fat.

period of time, a comparatively large amount of fat can be given. The changes produced are similar to those seen in human cases, namely, consolidation of the lung as the result of a hemorrhagic exudate into the alveoli and numerous fat emboli in lungs, brain and kidneys. The clinical symptoms which accompany these changes are predominatingly respiratory and cerebral. Though we did not succeed in reproducing the fall in hemoglobin, it was possible to duplicate the hemorrhagic exudate in the lung. Of the greatest significance was the demonstration of the fact that hydrolyzed fat is much more toxic than neutral fat and produced a far more intense hemorrhagic

exudate. It strongly suggests that the serious effect of fat embolism results in part from an alteration in the fat which renders it more irritating and that this change is of the nature of hydrolysis by lipases and that the fatty acid or resulting soaps are the irritative substances.

Mechanism Whereby Fat Embolism Develops.—Fat embolism occurs when free, fluid fat enters the vascular system and is carried by it to a capillary bed. There the globules of fat are sufficiently large to occlude the lumina of a greater or lesser number of the capillaries. Only under certain special circumstances can fat embolism occur. It is necessary first of all that fat be freed from fat cells. This implies some kind of trauma which will rupture the envelopes of the fat cells. Second, the fat must enter the venous circulation. As veins commonly collapse when they are opened, fat embolism will occur only under circumstances in which the sectioned veins remain open. But open veins bleed, and this implies a flow out of the vein rather than into it. Fat can enter veins only if it accumulates at a pressure greater than venous pressure and so is forced into the open vein. Three things, therefore, are necessary before fat embolism can occur: (1) An accumulation of fluid fat freed from its cellular envelope by trauma. (2) Open veins, the open ends of which do not collapse. (3) The accumulation of the fat under a pressure greater than venous pressure so that it can be forced into the open ends of the veins.

Though fat must be freed from its cellular envelope and veins cut across in many operations, and often by trauma, only under special circumstances do the veins remain open and the fat accumulate under a pressure sufficiently great to force its way into the veins. Injuries to bone provide exactly the factors necessary for the production of fat embolism. There is abundance of fat in the bone marrow easily set free by the trauma of fracture or operation. The veins are held open by their attachment to the bony haversian canals in which they run. It is not difficult for the wound exudate to accumulate under tension. In operations upon soft tissues, the reverse is the case. Though there is abundance of adipose tissue and though much fat may be freed, entrance into the veins is prevented by collapse of the veins and the diminished likelihood that the wound exudate will accumulate under tension. Exudate from soft tissue wounds seeps out along the line of suture. There is less opportunity for the application of firm dressings and hence less sealing of the exudate within the wound. Hence, fractures and operations upon bone constitute the most frequent antecedents of fat embolism.

Pathology of Fat Embolism.—Once fat has been forced into the venous system, it is carried by the circulation to the pulmonary capillaries. There a varying amount of occlusion occurs dependent upon the size of the globules, the total amount of fat which enters the circulation and the rate at which it reaches the lung. A small quantity of embolic fat will create less disturbance than a large quantity, and the same quantity introduced rapidly will produce severe or even fatal results, while introduced over a long period of time or in repeated small doses, it will cause little harm. In the lung the presence

of fat emboli occluding the pulmonary capillaries (1) interferes with normal oxygen exchange; (2) obstructs the pulmonary flow and hence causes dilatation of the right side of the heart; (3) causes an exudate into the alveoli. It has been noted by Grosskloss[1] and others that this exudate consists largely of erythrocytes and serum, but the accompanying fall in hemoglobin has not been recorded before.

The flood of embolic fat may be sufficiently great to cause death from pulmonary embolism in a short time. This accounts for certain deaths on the operating table or shortly after operation. In less severe cases, some of the pulmonary emboli are forced through the lungs and reach the systemic circulation through the left side of the heart. The fat again comes to rest in the systemic capillaries. The resultant symptoms are dependent upon the nature and importance of the organ whose capillaries are involved. Cerebral embolism is the most common, most important and most serious manifestation. In the brain, capillaries are occluded by the fat droplets, a narrow zone of brain tissue undergoes necrosis and the area of necrosis is surrounded by a zone of hemorrhage. This, in the gross, gives rise to the characteristic "ring hemorrhages." It is worthy of note that in the brain, as in the lung, the reaction induced by the fat emboli is hemorrhagic.

Though the cerebral lesions are the most important of the peripheral manifestations, emboli may occur in any organ. Two other sites of importance are the kidney and the skin, chiefly because they provide us with a means of diagnosis. Of the fat emboli which reach the kidney, a certain number rupture the glomerular capillaries and reach the urine where they can be recognized by appropriate measures. In the skin fat embolism produces a hemorrhagic reaction similar to that produced in the brain. The importance of these petechial skin hemorrhages lies in the strong confirmation they give to the diagnosis of fat embolism when the clinical syndrome suggests this complication.

SUMMARY.—The object in presenting a fatal case of fat embolism is to call attention to the existence of this complication of fractures and operations upon bones. Though of infrequent occurrence, it is of serious importance because of its high mortality. It is not easy to recognize either clinically or at postmortem for reasons which have been stated. The most valuable means of recognition still is the rather characteristic sequence of events in the clinical course: (1) An injury to a bone; (2) an interval in which the only symptoms are those related to the injured bone; (3) the development of pulmonary signs and symptoms; and (4) the development of cerebral signs and symptoms. Fat globules in the sputum and in the urine are of great diagnostic value in those cases in which they appear. Petechial hemorrhages in the skin are also of great diagnostic value when they occur.

To the somewhat meager group of signs and symptoms which are of diagnostic value we have added one further sign, namely, a profound fall in hemoglobin in an illness which complicates a fracture and follows the course outlined above. This sign is the result of the loss from the circulation of

great numbers of erythrocytes which are poured into the pulmonary alveoli in the hemorrhagic exudate which is called forth by the presence of fat emboli in the lung. It is worthy of note that in lung, brain and skin the characteristic response to fat embolism is a hemorrhagic exudate. The fall in hemoglobin noted in the two cases presented in this paper will occur only in those patients who have an extensive pulmonary exudate. Hence, we cannot expect to find it in every case of fat embolism. But when it does occur, and in company with the train of clinical events mentioned earlier, it is, like fat in sputum and urine and like petechial hemorrhages in the skin, strong confirmatory evidence of fat embolism. Those cases which are rapidly fatal from massive pulmonary fat embolism will not display it because there will not have been sufficient time to develop the hemorrhagic exudate. Similarly, the mild cases will not display it because the extent of the exudate is small. It will occur only in patients who sustain an extensive but not rapidly fatal fat embolism of the lung and who survive for a length of time sufficient for the development of extensive alveolar exudate. In such cases, however, it may be a valuable confirmatory sign of the disease.

The experiments we have conducted strongly suggest that the intensely irritating effect of fat embolism is the result of a change in the fat and that this change consists in the splitting of the fats by tissue lipases so as to free the irritating fatty acids. It will be necessary to develop these experiments further before definite conclusions can be reached.

CONCLUSIONS

(1) Fat embolism, though uncommon, is a more frequent complication of fracture and of operations on bone than is commonly supposed. An appreciation of its existence will lead to its more frequent recognition.

(2) It is difficult to recognize clinically because of the lack of specific and constant signs, and pathologically, because of the necessity of unusual staining methods.

(3) Points of value for diagnosis are: (a) The rather characteristic sequence of clinical events; (b) the occasional presence of fat in urine, fat in sputum and petechial hemorrhages in the skin. To this we would add, in certain cases, a profound fall in hemoglobin.

(4) The serious pathologic changes produced by fat emboli are probably due in part to the freeing of fatty acids by the action of tissue lipase.

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DISCUSSION.—DR. J. DEWEY BISGARD (Omaha, Neb.): This has been a most interesting presentation of a subject which I believe has received too little attention. My experience has been similar to that of Doctor Harris, that is, after becoming interested in the subject, I have seen much more clinical evidence of it.

Since the few cases of fat embolism which I have observed occurred in patients which had had either no anesthesias or anesthesias which contained no ether, and since ether is a fat solvent, the question of possible protection by ether against fat embolism was raised. Bone marrow fat from both tibiae of rabbits was macerated in a mortar and suspended in salt solution. This suspension was injected into the veins of the ears of other rabbits; in one group, during deep ether anesthesia, and in the other group of unanesthetized animals, which were used as controls. The lungs were examined for fat by Doctor Baker, a pathologist, and graded quantitatively by him with variations ranging from a trace up to four.

In the first group of animals there was a five-minute interval between injections and recovery of specimens. One cubic centimeter was injected, and the controls showed very much more fat than did the ones that received the injections while deeply anesthetized. Thirty minutes after injection of one cubic centimeter, there was still a striking difference between the controls and the etherized animals. Forty-eight hours later, however, the etherized group contained more fat than did the controls, and at 14 days, distinctly more.

Now, the question came up whether this fat passed on through into the peripheral circulation as a result of dilatation of the capillaries accompanying etherization, or whether the ether had some solvent action upon the fat. In answer to this question, we sectioned other tissues, liver, spleen, lung, brain, and heart, and in no instance did we find any fat emboli. Thus we concluded that the ether broke down the fat which circulated unobstructed until the ether was eliminated. As ether was given off in the lungs, the fat reappeared in the pulmonary capillaries in globules. When given intramuscularly, again the fat was found in the lungs, but in these instances principally in the alveoli, some in the capillaries, but in each instance in phagocytes. Apparently it was transported by these cells from the site of injection.

I made a series of experiments determining the influence of the tourniquet upon embolization of fat. Fat suspensions were injected into veins of the leg with the tourniquets applied above the sites of injection. The applications of the tourniquet for 15 minutes as compared to 45 minutes, resulted in much less fat in the 45-minute specimens. These observations were made with the veins closed and intact. Then studies were made with open veins; that is, after injection the veins were severed and the tourniquet removed either rapidly or slowly. In the latter, constriction was released to a degree that permitted arterial circulation to take place but yet maintained venous obstruction and caused considerable bleeding from the cut ends of the veins as compared to the lesser bleeding and lesser washing out of fat following the immediate release of the tourniquet. There was much less intravascular pulmonary fat in animals in which the tourniquet was released slowly.

The effect of drainage was investigated. Following wound drainage, distinctly less fat was found in the lungs than when the wounds were not drained and when the openings in the medullary canals were sealed with bone wax. In this latter group the medullary canal was opened and the fat macerated with a flexible probe.

As possible suggestions for aids to the prevention of fat embolism we might consider anesthesia as having some influence, ether a beneficial one possibly. I do not know. The use of a tourniquet during operation and slowly released afterwards minimizes the immediate influx of fat and may prevent an early postoperative catastrophe. Hemostasis is unquestionably helpful in minimizing the pressure accumulating within the medullary canal, which forces fat into the circulation, as is also drainage of the medullary canal for four days, again to relieve pressure. Gentle manipulation and rigid immobilization of

fractured and traumatized bone are recommended as time-honored, general fundamental principles.

Dr. Arthur W. Elting (Albany, N. Y.): Some ten years or more ago, I reported, before this Association, a study of fatal fat embolism to a rather incredulous audience, based on the subject matter of the paper, until we produced a series of slides which showed such a wide dissemination of fat throughout all the organs that even the most incredulous were willing to recognize that fat embolism was somewhat of an entity and might be a very serious one.

I expressed the view at that time, and I express it again to-day, based on a great deal of subsequent experience and careful observation, that fat embolism in a mild degree is of not infrequent occurrence. It does not always produce distinctive symptoms, it may not produce even suggestive symptoms, but to one who, in the language of Doctor Rodman when he spoke of being heart-minded, has occasion to treat cases of traumatism, if he is fat embolism-minded, he will be aware of more cases than if he does not think in those terms.

I may say that my original interest in this, of course, was first from a purely academic standpoint, but a case presented itself of a young man with a fractured humerus in whom, inside of 48 hours, rather serious complicating, apparent cerebral symptoms developed. I sought the assistance of Doctor Archambault, a noted neurologist, but I told him before he saw the patient that I would make the diagnosis for him because I had never seen a case of it, and, therefore, felt that I could make such a diagnosis, namely, that it was a case of fat embolism.

He was rather skeptical about my diagnosis. However, the patient eventually came to autopsy, after running a course exactly like that illustrated by the chart of the fatal case that Doctor Harris has reported. At autopsy, numerous petechial hemorrhages were found scattered generally throughout the body. They were not noticeable on the surface of the body, however, and the pathologist drew the conclusion that we were dealing with a rapidly fulminating Streptococcic infection. I still clung to my diagnosis, and of course they saw no evidence of fat. I insisted that the tissues must all be stained for fat, and in a few days he reported to me that the smaller vessels were uniformly plugged with fat throughout the organs studied.

I felt as a basis of our study, and I feel to-day as a basis of our continued observation, that fat embolism manifests itself in different forms, in varying degrees. I have regarded the pulmonic form as perhaps the more frequent one, the cerebral form as usually or very apt to represent a final stage. I also feel that the age of the individual has a good deal to do with this.

A few years ago, one of my assistants cared for a simple fracture of a tibia in a small child, six or eight years of age. He thought it was desirable to perform an open reduction because of serious displacement and inability to reduce the fracture. In some 48 hours the child's temperature went up pretty high and it showed the evidences of what was supposed to be infection. At the same time the patient became quite disoriented and evidenced some cerebral symptoms. I was asked to see the case and looked at the wound. It seemed to look all right, and I made a diagnosis of cerebral fat embolism. The next day the child was in deep coma and apparently dying. I remember showing that case at one of my clinics as a typical case of fat embolism. I ventured the prognosis that in spite of the deep coma, because of the youth of the patient that recovery would be probable. Fortunately, I guessed right. In a few days the coma lessened very much as in the case of Doctor Harris' recovery, and the child got well.

I found from my study at that time that there was a conviction among

certain writers that in youth fat embolism is not nearly so serious a malady as in those of more advanced age. Furthermore, it seemed evident that fat embolism did not depend upon the extent or severity of the traumatism. That, it seems to me, has always been a remarkable feature. Many times since then, however, we have seen, and I am sure you have all seen, mild cerebral disturbances, a little disorientation, a little delirium, and mild, unexplainable cerebral disturbances during the days following an injury or fracture, where perhaps you have offered no particular explanation.

I found shock and infection were two of the diagnoses often made in cases I believed to have been instances of fat embolism. Furthermore, unless the surgeon has it in mind, and unless he insists that the pathologist especially examines the tissues for fat, it is not going to be recognized. We have found very serious fat embolism in cases in which we believed it played a rôle in death as well as in cases who died from other causes after severe traumatisms of bone, simply because the pathologist was made fat-minded and felt that he had to give an excuse if he did not supply us with a very good reason for not examining the tissues, especially the lungs, the brain and the kidneys for fat. It will also be found in the pancreas, the heart and all the other organs if pains are taken to look for it.

I feel it is an important matter to again have our memory refreshed. I have been wondering, during these years since I made my original report, why fat embolism received so little attention, because I cannot think that we have had anything particularly unique in our relatively limited experience in so small a community as Albany.

Dr. William Darrach (New York): During the last ten years, over 12,000 fractures have been treated on the Fracture Service of the Presbyterian Hospital. Of these, two cases have shown evidences of fat embolism. One of these is herewith reported.

Case Report.—C. B., female, age 72, was admitted to the hospital, November 22, 1937, having been knocked down by an automobile one hour previously, and suffered a compound fracture of both bones of the left leg, fracture of distal third left ulna, a scalp wound and cerebral concussion. She was transported by ambulance, a Thomas splint having been previously applied. On arrival, she was confused and in moderate shock. After rest, heat, two infusions of 500 cc. each of Ringer's solution, a transfusion of 300 cc. and 10 cc. of eschatin, she was taken to the operating room and the compound wound of the leg débrided, the fracture reduced through a separate incision and a four-screw, stainless steel plate applied to the tibia. Both wounds were packed with vaseline gauze and left open. A closed reduction was carried out with the ulnar fracture. The scalp wound was débrided and closed. She was returned to bed in very good condition.

A second transfusion was given the following afternoon. For the following 24 hours the patient was restless and somewhat disoriented with some stiffness of the neck. Whether this was due to lame muscles from her injury or to subarachnoid irritation was not known. At this time, her temperature was 101° F., pulse 110, respirations 30. The second day after operation her temperature gradually rose to 102° F., pulse 120, respirations 36. There was almost no cyanosis or air hunger. On the morning of the third day she became more comatose and more cyanotic. Respirations were 26, with an increase of rigidity of her neck. Coarse, moist râles were heard at both bases. Seventy-two hours after injury, the lung sounds became much more moist with many coarse râles, cyanosis increased, her pulse remained strong and regular. Four hours later she suddenly stopped breathing. She died apparently from respiratory failure. Except for a heavy trace of albumin and a few casts, the urine was normal, no fat being found.

Autopsy showed extensive fat emboli of the pulmonary capillaries with marked

stasis and a very early inflammatory reaction (Fig. 1). Frozen section of the brain showed no fat emboli.

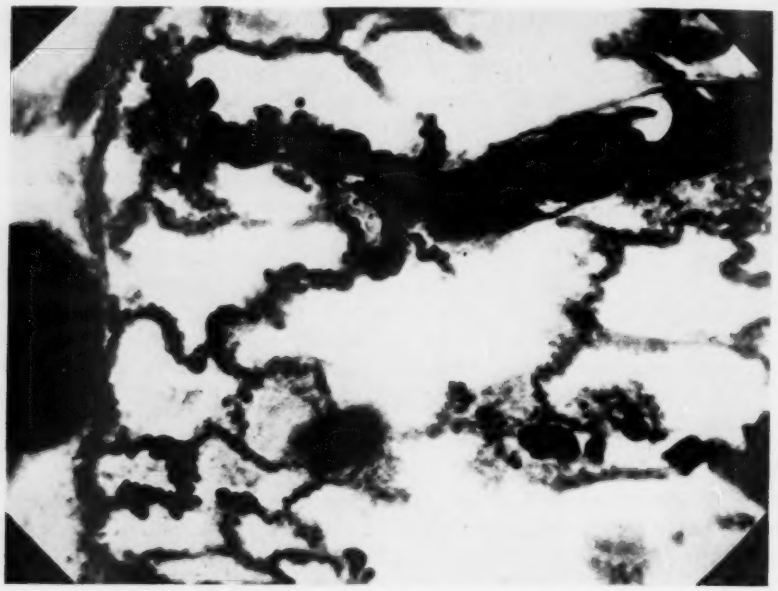

FIG. 1.—Photomicrograph of lung showing extensive fat emboli in the pulmonary capillaries, marked stasis, and an early inflammatory reaction.

DR. ROBERT I. HARRIS (Toronto, Canada): I am grateful to Doctor Bisgard for bringing to my attention, and to the attention of this Association, the work he has done on fat embolism. The subject is so inherently difficult, and so obscure in its manifestations, that it is much in need of investigation which will elucidate the obscure aspects of the disease.

In my paper I deliberately avoided any discussion of treatment, wishing to concentrate upon what I felt was a new manifestation of the disease, even though it was of minor significance. My feeling is that any additional sign which might facilitate the diagnosis of fat embolism was worth reporting and recording.

If I were to say anything about treatment, it would be that measures designed to remove the hematoma and its associated fat should be the background of treatment. That is to say, drainage of areas of operation upon bone, the use of a tourniquet during operations upon bone, and aspiration of any hematoma about a fracture.

I am grateful also to Doctor Elting for his contribution to the discussion, and if I may, with his consent, carry on the torch of the fat embolists, I shall be proud to do so.

REPORT ON THE AMERICAN BOARD OF SURGERY*

EVARTS A. GRAHAM, M.D.
ST. LOUIS, MO.

THERE have been so many questions asked about the activities of the American Board of Surgery, or rather, about the progress which is being made, that the officers of the Association felt it was desirable to have a statement made at this meeting.

I should like to say first of all that there were 1,570 applications received for the Founders Group of the Board. Of this number, after careful scrutiny in every way that the Board knew how to make of the fitness of these men for membership, certificates were given to 938. That is approximately 60 per cent of those who applied. I might say, however, that that is not really a fair indication because of those who merely sent in applications and who had not already demonstrated the superior training and ability in surgery by being a member of the component organizations or by holding a professorship or an associate professorship in one of the recognized medical schools, a much larger percentage than 40 per cent were rejected. I cannot give you the exact figure of that number.

There have been 423 candidates submitted to examination, excluding 86 who have just been examined in New York during the first three days of this week. Of this number there have been 205 who have finished Part II of the examination; the rest were examined only in Part I.

There were 29.3 per cent failures in the examination. Possibly some of you may think this is not a high enough mortality; others may think that perhaps the mortality is excessive. At any rate, for the benefit of those who think that perhaps the mortality is not sufficiently high, I wish to call your attention to the fact that this examination represents really the third hurdle that the men have gone over who have taken it. The first hurdle, is as careful a scrutiny as the Board can possibly make concerning the man's fitness to take the examination, that is determining his previous training, *etc.*

The second hurdle, is a personal inspection of a man's performance in the operating room, carried out either by a member of the Board or by some man already certificated by the Board in whom the Board has confidence.

There have been a considerable number of rejections along the way. Therefore, when I state that there have been 30 per cent of failures in the examination, it would probably be more fair to say that 40 to 50 per cent of those men who have applied for the privilege of taking the examination have failed to make the grade.

There are certain things that have come out that are of considerable interest in these examinations, and I would like to take a minute or two to dwell upon

* Read before the American Surgical Association, Hot Springs, Va., May 11, 12, 13, 1939.

at least one of these points, because it is a matter which I think concerns every one of us here who is concerned in any way with the teaching of surgery. We have found that, as a whole, the men are fairly good on their clinical surgical work. We have found that they are also fairly good in the examination which is given them in anatomy. We find that in pathology, however, they are *astoundingly* weak, to a degree which is almost unbelievable.

I should like to say something about my own experience, for instance, last Monday in this examination in New York. As part of the gross tissues which we had for examination by candidates, I had a fresh, nodular thyroid which had been removed only two or three hours before. The specimen was in excellent condition, and looked exactly like a specimen that had just been removed from the patient. There was nothing especially unusual about it. I examined nine candidates, to all nine of whom I showed this specimen, because of the remarkable display of ignorance of gross pathology which the first candidate had shown. The first candidate whom I had, told me that this specimen was probably a pancreas. I asked him if there was anything the matter with it, and he said no, he would regard it as a normal pancreas.

Incidentally, with references to what has just gone on here before, I might say that I said, "Well, then, you think this is probably an autopsy specimen?" He said, "No, I understand that Doctor Whipple is removing the pancreas! This was probably removed at operation"—but it was regarded as a normal pancreas.

The next man who saw this specimen said it was clearly a lipoma. A third man, not in succession but a little later in the series, said that he was not able to tell from what part of the intestine it had come, but obviously it was from the intestine, because it had intestinal mucous membrane on it.

I do not know what the explanation is of such appalling ignorance in gross pathology. I would have thought, before personal experience with these examinations—we have had six of them now—that such a thing would have been impossible on the part of anyone who was performing general surgery.

I might say that these three men were not men who confine their work, we will say, to fractures or orthopedic work, or something of that sort, but they were men who were trying to qualify themselves in general surgery, including thyroid work.

My experience was not unique. The experience of all the other examiners was practically the same as regards pathology, and neither was the experience in New York unique. We have met with that experience all over the country where we have given these examinations.

The importance of this observation, it seems to us who are teachers and who are conducting services for the graduate training in surgery, is that we must see to it that men who are spending a number of years in getting a graduate training in surgery, must have during their course of training sufficient experience in gross pathology to avoid such catastrophic ignorance as many of these men are presenting.

We do fail these men in their pathology when they make the deplorable

exhibits of themselves as these men have, and we compel them to take a re-examination in pathology. This has had a very wholesome effect. Some men who have failed in pathology, for instance, at a previous examination, come up again for a new examination with the statement that now they have spent a year learning pathology, and I think almost without exception they have made a very creditable performance on their second appearance.

I might say in reference to this fact, also, we have positive knowledge that in many instances courses of graduate training in surgery have been altered so as to provide for those men who are being trained in surgical careers, during their hospital work, long periods of uninterrupted time when they will get a pretty sound training in pathology, both gross and microscopic.

I look upon this observation, which I have just cited in reference to pathology, as a most astounding discovery. I would not have thought that it was possible that young surgeons who otherwise have obtained a pretty good training, could have been so deficient in one of the fundamental features of surgery, namely, pathology. I feel that the fact that the Board has made this discovery will accomplish much good, and that if it has not accomplished anything else, the fact that it has noted the woeful lack of pathologic training has perhaps more than justified its existence.

I would like to say one more thing. This is in defense of the Board. There have been many criticisms of all kinds; you could not possibly think of one that has not been leveled against the Board. The Board is glad to receive these criticisms and to do what it can to correct them. We have been in existence only a little more than two years. We realize that the whole business is somewhat experimental from the standpoint of its operation. We realize that changes will have to take place in the ultimate procedure of qualifying men for this certificate. We do, however, hope that you will realize that this is an enormous task, that all of the members of the Board spend a very great amount of time on this work. We are very glad indeed to do it. We do not mind receiving the blows and the criticisms from it, but we do hope that you will be perhaps somewhat charitable toward us for a year or two longer until we can get the whole affair working in a more efficient way.

When I state that we have been working hard, I wish to tell you that the Board meets at least twice a year, and generally three times, for periods of three or four days. The work of the Board runs continuously from nine o'clock in the morning until eleven o'clock at night, except for usually about an hour for lunch and an hour for dinner. Those of us who are ordinarily actively walking around and standing on our feet feel it a hard task to sit down for so long a period of time.

BRIEF COMMUNICATION AND CASE REPORT

FATAL PULMONARY EMBOLISM FROM SUPERFICIAL THROMBOPHLEBITIS

CASE REPORT

D. Woolfolk Barrow, M.D.

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Ligation of a superficial vein proximal to an area of superficial thrombophlebitis has been advocated by Bancroft[1] Edwards,[2] Eisenklamm,[4] Faxon,[5] Freeman,[6] Homans,[7, 8] O'Neil,[10] Sears,[11] Stone,[12] and others, not only because it affords symptomatic relief, but also because it is believed it lessens the likelihood of pulmonary embolus. The following case report emphasizes the importance of such a prophylactic surgical procedure:

Case Report.—F. O. B., white, female, age 49, was admitted to the New Orleans Charity Hospital October 14, 1938, complaining of pain in the left leg of 11 days' duration. This had begun after bruising the left calf, 11 days previously. The pain was confined to the lower leg at first, but, at the time of admission, it had extended to the groin, and was aggravated by walking. The patient said she had had five mild chills prior to entry.

Twenty-eight years previously, soon after the birth of her first child, the patient had had a sudden onset of tremendous swelling and discomfort in her left leg. A diagnosis of phlegmasia alba dolens (milk-leg) was made. Her immediate discomfort was relieved by rest in bed, but ever since that time the patient had noticed dilated, tortuous superficial veins of the left leg. Subcutaneous rupture of one of the varices resulted in localized pain and a residual hematoma which was slowly absorbed. Subsequently she had a similar episode. There had been no ulceration of the leg. Five years before entry, the patient had a cholecystectomy and incidental appendicectomy performed, without postoperative complications. She had had whooping cough, chickenpox, measles, malaria, and rheumatic fever in childhood.

Physical Examination.—The patient was obese, and was able but reluctant to walk because of the aggravation of pain which this caused in her left leg. The left leg showed multiple, tender, nodular, cord-like swellings along the course of both the long and short saphenous veins. The left calf was slightly larger than the right, and the subcutaneous tissues were indurated. There was no detectable difference in temperature on the two sides. The dorsalis pedis arteries on both legs were readily palpable. Blood pressure 150/90. Pulse on admission was 103 and varied from 80 to 103 during the course of her stay in the hospital. Temperature was 97.7° F. on admission and varied between 97.7° and 100° F. White blood count 14,500 on admission; urine negative.

Subsequent Course.—Ligation of the saphenous vein was proposed, but was not carried out, not only because it was felt that the thrombi were too widespread to be favorably affected, but also because the patient's symptoms subsided so rapidly on con-

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servative treatment. Although the patient was anxious to go home she was kept in bed, since localized tenderness remained.

On the fourteenth day at 5:30 A.M. the patient experienced sudden pain under the sternum immediately after exerting herself to get on the bed pan. The pain was followed by profuse sweating, dyspnea, cyanosis and death in a very few minutes.

Autopsy.—The superficial veins of the left leg were irregularly distended and contained firm clots. These did not extend into the deep venous system at any point. On microscopic examination the clots were found to be partially organized.

The lungs were reddish-purple in color, boggy in consistency, and weighed 1,300 Gm. On section the entire parenchyma was edematous. The bronchial tree and hilar lymph nodes were normal. A loose fitting thrombus filled the pulmonary artery and extended into the left main branch. The inferior vena cava, portal vein, iliac vein and femoral vein contained no thrombi. The pathologist, on the basis of his examination, felt that the pulmonary embolus arose from the left great saphenous vein.

Although such serious sequelae following superficial thrombophlebitis are not commonly found, Nobl[9] found that 0.5 per cent of fatal pulmonary emboli arise in superficial veins. Proximal ligation of such a superficial thrombophlebitic vein would not only minimize the danger of such a disastrous complication, but has, in our experience, relieved the patient's symptoms. Furthermore, since destruction of venous valves seems to be an inevitable sequela to thrombophlebitis,[3] the affected vein, if not already varicosed, will become so, so that ligation will eventually be necessary, the technic of which should follow the accepted surgical methods of treatment for varicosities of the group of veins so affected.[11] We have not encountered wound infection in patients thus treated nor has it been reported in the literature.

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FINNEY-HOWELL RESEARCH FOUNDATION, INC.

ANNOUNCEMENT has been made by the Finney-Howell Research Foundation, Inc., that all applications for fellowships for next year must be filed in the office of the Foundation, 1211 Cathedral Street, Baltimore, Md., by January 1, 1940. Applications received after that date cannot be considered for 1940 awards, which will be made the first of March, 1940.

This Foundation was provided for in the will of the late Dr. George Walker of Baltimore for the support of "research work into the cause or causes and the treatment of cancer." The will directed that the surplus income from the assets of the Foundation together with the principal sum should be expended within a period of ten years to support a number of fellowships in cancer research, each with an annual stipend of two thousand dollars, "in such universities, laboratories and other institutions, wherever situated, as may be approved by the Board of Directors."

Fellowships carrying an annual stipend of $2000 are awarded for the period of one year, with the possibility of renewal up to three years; when deemed wise by the Board of Directors, special grants of limited sums may be made to support the work carried on under a fellowship.

Applications must be made on the blank forms which will be furnished by the Secretary or any member of the Board of Directors.

October 16, 1939.

CORRECTION

In the article by Dr. John deJ. Pemberton: Reactions Following Operations for Hyperthyroidism. Annals of Surgery, **104**, 507-512, October, 1936, the concentration of sodium citrate was erroneously reported. The last four lines, page 512, should have read: "In two of the cases of exophthalmic goiter marked clinical improvement apparently resulted from the intravenous administration of a solution of 0.5 per cent sodium citrate and 0.9 per cent sodium chloride to which was added an active preparation of cortin."

EDITORIAL ADDRESS

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INDEX TO VOLUME 110

A

ABBOTT, LEROY C.: Operative Lengthening of Tibia and Fibula, 961.
Abdominal Lesions, Circulatory Problems of Surgical Importance in Diagnosis of, 766; Surgery, Spinal Anesthesia in, 863.
Abscess, Left Subphrenic, 562.
Abscesses, Retropharyngeal and Lateral Pharyngeal, 177.
Acid, Dehydrocholic, Effect of, Upon Biliary Pressure and Its Clinical Application, 67.
Acoustic Neuromata, Total and Intracapsular Extirpation of, 513.
Acute Intestinal Obstruction, Effect of, on the Blood and Plasma Volumes, 25.
Address, Presidential, 481.
Adenocarcinoma of the Transverse Colon in a Boy Age Fifteen, 472.
Advantages, Demonstrable and Technic, of the Devine Colostomy, 14.
Agenesis, Unilateral, of Müllerian System in the Female, 316.
Agents, Assay of General Anesthetic, 823.
Air, Sterilization of, with Bactericidal Radiant Energy, 291.
ALLEN, A. W.: Control of Postoperative Bleeding in Obstructive Jaundice, 693.
American Board of Surgery, Report on, 1115.
Anesthesia, Intravenous and Regional, 878; Morphine and Cyclopropane, Use of Barbiturates in Preventing Cardiac Irregularities Under Cyclopropane or, 84; Present Status of Spinal, 851; Spinal in Abdominal Surgery, 863; Spinal, for Thoracoplasty, Further Experiences in Use of, 872; Sympathetic Nerve Block as Adjunct, in Minimal Resection of Stomach for Peptic Ulcer, 886; Trends in Inhalation, 830.
Anesthetic Agents, Assay of General, 823.
Anesthetics and Drugs, Influence of Certain, Upon Gastro-intestinal Tone and Motility, 802.
Aneurysm, Arteriovenous, of the Neck, 131; of External Carotid Artery with Carotid Sinus Reflex, 133; Intracranial Arteriovenous, 525.
Ankle Malunion, Treatment of, 447.
Announcement of Third International Cancer Congress, 319.
Anoxia, 835.
Anus, Artificial, with Mechanical Sphincter, 311.
Appendicitis, Acute, with Perforation, Primary Closure of Peritoneum in, 222; in Man, Experimental Proof of Obstructive Origin of, 629; Ruptured, Paratyphoid Fever Complicated by, 466.
Application of Carbamide (Urea) Therapy in Wound Healing, 94.
Arteries, Two Cystic, and Two Cystic Ducts, Double Gallbladder with, 60.
Arteriosus, Patent Ductus, Surgical Management of, 321.
Arteriovenous Aneurysms, Intracranial, 525; of the Neck, 131.
Artery, Aneurysm of External Carotid, with Carotid Sinus Reflex, 133; and Vein, Nutrient, Disruption of, Effect on Bone Marrow of, 940.
Artificial Anus with Mechanical Sphincter, 311.
Ascites, Chylous, 140; and Hydrothorax, Fibroma of the Ovary with, 731.
Assay of General Anesthetic Agents, 823.
Avulsed Skin Flaps, Treatment of, 951.

B

Bactericidal Radiant Energy, Sterilization of Air with, 291.
BAILEY, FRED W.: Obituary of Francis Reder, 149.
Balance, Water and Electrolyte, Control of, in Surgical Patients, 1050.
BALFOUR, DONALD C.: Obituary of Sir Thomas Myles by, 790.
Barbiturates, Use of, in Preventing Cardiac Irregularities Under Cyclopropane or Morphine and Cyclopropane Anesthesia, 84.
BARKER, M. HERBERT: Clinical and Experimental Experiences in the Surgical Treatment of Hypertension, 1016.
BARROW, D. WOOLFOLK: Fatal Pulmonary Embolism from Superficial Thrombophlebitis, 1118.
BARTLETT, WILLARD: Obituary of Ellis Fischel, 156.
BAXTER, JAMES H., JR.: Use of Barbiturates in Preventing Cardiac Irregularities Under Cyclopropane or Morphine and Cyclopropane Anesthesia, 84.
BEECHER, HENRY K.: Assay of General Anesthetic Agents, 823.
BERNHARD, A.: Significance of Cholesterol Partition of Blood Serum in Surgery of the Gallbladder, 701.
BEST, R. RUSSELL: Effect of Dehydrocholic Acid Upon Biliary Pressure and Its Clinical Application, 67.

Bile Duct, Common, Primary Carcinoma of the, 474; Double Common, with Choledochus Cyst, 55.
Bile from the Liver, Effect of Distention of Colon and Stimulation of Its Nerve Supply on Flow of, 755.
Biliary Fistulae, Internal, and Intestinal Obstructions Due to Gallstones, 50; Pressure and Its Clinical Application, Effect of Dehydrocholic Acid Upon, 67.
BINNEY, HORACE: Extrapleural Pneumothorax, 578.
BISGARD, J. DEWEY: Influence of Certain Drugs and Anesthetics Upon Gastrointestinal Tone and Motility, 802.
BLAIR, VILRAY P.: Obituary of John Roberts Caulk, 151.
BLALOCK, ALFRED: Myasthenia Gravis and Tumors of Thymic Region, 544.
Bleeding, Control of Postoperative, in Obstructive Jaundice, 693.
Blood, and Plasma Volumes, Effect of Acute Intestinal Obstruction on the, 25; Serum in Surgery of the Gallbladder, Significance of Cholesterol Partition of the, 701.
Board of Surgery, American, Report on, 1115.
BOLDREY, EDWIN B.: Dermoid Cysts of the Vertebral Canal, 273.
Bone, Solitary Myeloma of, 427; Marrow, Effect on, of Disruption of Nutrient Artery and Vein, 940.
BOOK REVIEW: Modern Surgical Technic by Max Thorek, Reviewed by Merrill N. Foote, 158; Operative Orthopedics by Willis C. Campbell, Reviewed by Robert L. Preston, 800; Surgical Pathology of the Mouth and Jaws by Arthur E. Hertzler, Reviewed by Irving M. Derby, 480.
BOOKS RECEIVED, 320.
BOURNE, WESLEY: Further Experiences in Use of Spinal Anesthesia for Thoracoplasty, 872; Trends in Inhalation Anesthesia, 830.
Bowel Obstruction in the New Born, 587.
BROWDER, JEFFERSON: Revaluation of Treatment of Head Injuries, 357.
BROWN, W. EASSON: Spinal Anesthesia in Abdominal Surgery, 863.
BUCHANAN, EDWIN P.: Chylous Ascites, 140.
Burrowing, Undermining, Chronic Ulcers Due to the Micro-aerophilic Hemolytic Streptococcus, Combined Use of Zinc Peroxide and Sulfanilamide in Treatment of, 1067.
BUSH, LEONARD F.: Present Status of Spinal Anesthesia, 851.

C

CAMPBELL, WILLIS C.: Use of Vitallium as Material for Internal Fixation of Fractures, 119.
Canal, Vertebral, Dermoid Cysts of the, 273.
Cancer Congress, Announcement of Third International, 319.
Carbamide (Urea) Therapy, Application of, in Wound Healing, 94.
Carcinoma, of the Colon and Rectum, 1; Primary, of the Common Bile Duct, 474.
Cardiac Irregularities, Use of Barbiturates in Preventing, Under Cyclopropane or Morphine and Cyclopropane Anesthesia, 84.
Carotid Artery, Aneurysm of External, with Carotid Sinus Reflex, 133.
CARP, LOUIS: Fractures and Dislocations by Muscular Violence Complicating Convulsions Induced by Metrazol for Schizophrenia, 107.
CARTER, BURR N. Left Subphrenic Abscess, 562.
Cascara Sagrada, Melanosis Coli, An Attempt at Its Experimental Production by Repeated Administration of, 461.
Cavernous Hemangioma of a Cervical Nerve, 138.
Cecostomy as Complementary and Decompressive Operation, 380.
Cervical Nerve, Cavernous Hemangioma of a, 138.
CHERNEY, LEONID S.: Unilateral Agenesis of the Müllerian System in the Female, 316.
Choledochus Cyst with Double Common Bile Duct, 55.
Cholesterol Partition of the Blood Serum in Surgery of the Gallbladder, Significance of, 701.
Chondritis of Knee, 948.
Chronic Ulcers Due to Micro-aerophilic Hemolytic Streptococcus, Combined Use of Zinc Peroxide and Sulfanilamide in Treatment of, 1067.
Chyle Cysts, Retroperitoneal, 389.
Chylous Ascites, 140.
Circulatory Problems of Surgical Importance in the Diagnosis of Abdominal Lesions, 766.
CLARK, DWIGHT E.: Significance of Lipocaic in Surgery, 907.
Clinical Consideration of Methods of Equalizing Leg Length, 992; and Experimental Experiences in the Surgical Treatment of Hypertension, 1016.
Closure, Primary, of Peritoneum in Acute Appendicitis with Perforation, 222.
Coli, Melanosis, 461.
Colon, Effect of Distention of the, and Stimulation of Its Nerve Supply on Flow of Bile from the Liver, 755; and Rectum, Carcinoma of the, 1; Transverse, Adenocarcinoma of the, in a Boy Age Fifteen, 472.
Colostomy, Devine, Technic and Demonstrable Advantages of the, 14; Value of Preliminary, in Correction of Gastrojejunocolic Fistula, 659.
COLP, RALPH: Ileocolostomy with Exclusion, 648; Obituary of Edwin Beer by, 795.

Common Bile Duct, Double, with Choledochus Cyst, 55; Primary Carcinoma of the, 474.
Congenital Cystic Kidney Treated by Ureteral Drainage, 231.
Congress, Anouncement of Third International Cancer, 319.
Contracture, Volkmann's Ischemic, Treatment of, 417.
Control, of Postoperative Bleeding in Obstructive Jaundice, 693; of Water and Electrolyte Balance in Surgical Patients, 1050.
Convulsions Induced by Metrazol for Schizophrenia, Fractures and Dislocations by Muscular Violence, Complicating, 107.
Correction, 480; of John Pemberton article, 1120.
CORWIN, WARREN C.: Melanosis Coli: An Attempt at Its Experimental Production by Repeated Administration of Cascara Sagrada, 461.
Cranial Defects, Repair of, by Cranioplasty, 488.
Cranioplasty, Repair of Cranial Defects by, 488.
Cure of Flatfoot, Operation for, 437.
Cyclopropane, Use of Barbiturates in Preventing Cardiac Irregularities Under, or Morphine and Cyclopropane Anesthesia, 84.
Cyst, Choledochus, with Double Common Bile Duct, 55; Spinal Extradural, Associated with Kyphosis Dorsalis Juvenilis, 285.
Cystic Ducts, Two, and Two Cystic Arteries, Double Gallbladder with, 60; Kidney, Congenital, Treated by Ureteral Drainage, 231.
Cysts, Dermoid, of the Vertebral Canal, 273; Retroperitoneal Chyle, 380.

D

DANDY, WALTER E.: Papilledema without Intracranial Pressure, 161.
DARRACH, WILLIAM: Chondritis of Knee, 948.
DAVIS, LOYAL: Clinical and Experimental Experiences in the Surgical Treatment of Hypertension, 1016.
Decompressive and Complementary Operation, Cecostomy as, 380.
Defects, Repair of Cranial, by Cranioplasty, 488.
Dehydrocholic Acid, Effect of, Upon Biliary Pressure and Its Clinical Application, 67.
DENNIS, CLARENCE: Experimental Proof of Obstructive Origin of Appendicitis in Man, 620.
DERBY, IRVING M.: Review of Arthur E. Hertzler's Surgical Pathology of the Mouth and Jaws, 480.
Dermoid Cysts of the Vertebral Canal, 273.
Development of National Surgical Societies, 481.
Devine Colostomy, Technic and Demonstrable Advantages of the, 14.
Diabetic, Gangrene of the Extremity in the, 723.
Diagnosis of Abdominal Lesions, Circulatory Problems of Surgical Importance in, 766.
Digital Extensor Tendons, Habitual Dislocation of the, 81.
Discussion of Multiple Neurofibromatosis, 916.
Dislocation, Habitual, of the Digital Extensor Tendons, 81.
Dislocations and Fractures by Muscular Violence Complicating Convulsions Induced by Metrazol for Schizophrenia, 107.
Disruption of Nutrient Artery and Vein, Effect on Bone Marrow of, 940.
Distention of the Colon, Effect of, and Stimulation of Its Nerve Supply on Flow of Bile from the Liver, 755.
Double Common Bile Duct, Choledochus Cyst with, 55; Gallbladder with Two Cystic Ducts and Two Cystic Arteries, 60.
DRAGSTEDT, LESTER R.: Significance of Lipocaic in Surgery, 907.
Drainage, Ureteral, Congenital Cystic Kidney Treated by, 231.
Drugs and Anesthetics, Influence of Certain, Upon Gastro-intestinal Tone and Motility, 802.
Duct, Double Common Bile, with Choledochus Cyst, 55.
Ductus Arteriosus, Patent, Surgical Management of, 321.
Duodenal Ulcer, Study of Results of Medical Treatment of, 37.
Duodenal and Recurring Ulcer, Lateral Gastroduodenostomy in Cases of, 622.

E

Effect of Acute Intestinal Obstruction on the Blood and Plasma Volumes, 25; on Bone Marrow of Disruption of Nutrient Artery and Vein, 940; of Dehydrocholic Acid Upon Biliary Pressure and Its Clinical Application, 67; of Distention of the Colon and Stimulation of Its Nerve Supply on Flow of Bile from the Liver, 755.
EGGERS, CARL: Obituary of Franz J. A. Torek, by, 707.
Electrolyte and Water Balance, Control of, in Surgical Patients, 1050.
Electrosurgical Operation for Excision of a Hydrocele Sac, 314.
ELKIN, D. C.: Hurthle Cell Tumors of the Thyroid, 160.
ELKINTON, J. RUSSELL: Control of Water and Electrolyte Balance in Sugical Patients, 1050.
ELOESSER, LEO: Obituary of Emmet Rixford, by, 786.
ELTING, ARTHUR W.: Obituary of John Lawrence Yates by, 792.

ELVIDGE, ARTHUR R.: Dermoid Cysts of the Vertebral Canal, 273.
Embolism, Fat, 1095; Fatal Pulmonary, from Superficial Thrombophlebitis, 1118.
Energy, Bactericidal Radiant, Sterilization of Air with, 291.
Equalizing Leg Length, Clinical Consideration of the Methods of, 992.
ESSER JOHANNES F. S.: An Artificial Anus with Mechanical Sphincter, 311.
Evisceration Causing Rupture of Jejunum, 464.
Excision of a Hydrocele Sac, Electrosurgical Operation for, 314.
Exclusion, Ileocolostomy with, 648.
Experiences, Clinical and Experimental, in the Surgical Treatment of Hypertension, 1016; in Use of Spinal Anesthesia for Thoracoplasty, 872.
Experimental and Clinical Experiences in the Surgical Treatment of Hypertension, 1016; Proof of Obstructive Origin of Appendicitis in Man, 629.
Extensor Tendons, Digital, Habitual Dislocation of the, 81.
External Carotid Artery, Aneurysm of, with Carotid Sinus Reflex, 133.
Extirpation, Total and Intracapsular, of Acoustic Neuromata, 513.
Extradural Cyst, Spinal, Associated with Kyphosis Dorsalis Juvenilis, 285.
Extrapleural Pneumothorax, 578.
Extremity, Gangrene of the, in the Diabetic, 723.

F

FARMER, ALFRED W.: Treatment of Avulsed Skin Flaps, 951.
Fat Embolism, 1095.
Fatal Pulmonary Embolism from Superficial Thrombophlebitis, 1118.
Female, Müllerian System in the, Unilateral Agenesis of, 316.
Fever, Paratyphoid Complicated by Ruptured Appendicitis, 466.
Fibroma of the Ovary with Ascites and Hydrothorax, 731.
Fibula and Tibia, Operative Lengthening of, 961.
FINE, JACOB: Effect of Acute Intestinal Obstruction on the Blood and Plasma Volumes, 25; The Rôle of the Nervous System in Acute Intestinal Obstruction, 411.
FINLAYSON, ALISTER I.: Effect of Dehydrocholic Acid Upon Biliary Pressure and Its Clinical Application, 67.
Finney-Howell Research Foundation, Inc., Notice of, 1120.
Fistula, Gastrojejunocolic, Value of Preliminary Colostomy in Correction of, 659.
Fistulae, Internal Biliary, and Intestinal Obstructions Due to Gallstones, 50.
FITZGERALD, R. R.: Habitual Dislocation of the Digital Extensor Tendons, 81.
FITZHUGH, O. GARTH: Use of Barbiturates in Preventing Cardiac Irregularities Under Cyclopropane or Morphine and Cyclopropane Anesthesia, 84
Fixation of Fractures, Internal, Use of Vitallium as Material for, 119.
Flaps, Treatment of Avulsed Skin, 951.
Flatfoot, Operation for Cure of, 437.
FLOOD, CHARLES A.: Study of Results of Medical Treatment of Duodenal Ulcer, 37.
FOOTE, MERRILL N.: Review of Modern Surgical Technic, by, 158.
FOSS, HAROLD L.: Present Status of Spinal Anesthesia, 851.
Fractures, and Dislocations by Muscular Violence Complicating Convulsions Induced by Metrazol for Schizophrenia, 107; Internal Fixation of, Use of Vitallium as Material for, 119.

G

Gallbladder, Double, with Two Cystic Ducts and Two Cystic Arteries, 60; Surgery of the, Significance of Cholesterol Partition of the Blood Serum in, 701.
Gallstones, Internal Biliary Fistulae and Intestinal Obstructions Due to, 50.
Gangrene, Gas, 100; of the Extremity in the Diabetic, 723.
GARLOCK, JOHN H.: Primary Carcinoma of the Common Bile Duct, 474.
Gas Gangrene, 100.
Gastrocolic Omentum and Transverse Mesocolon, Hernia Through, 456.
Gastroduodenostomy, Lateral, in Cases of Duodenal and Recurring Ulcer, 622.
Gastro-intestinal Tone and Motility, Influence of Certain Drugs and Anesthetics Upon, 802.
Gastrojejunocolic Fistula, Value of Preliminary Colostomy in Correction of, 659.
GENDEL, SAMUEL: Effect of Acute Intestinal Obstruction on the Blood and Plasma Volumes, 25; The Rôle of the Nervous System in Acute Intestinal Obstruction, 411.
General Anesthetic Agents, Assay of, 823.
GERBODE, F.: Sclerosing or Retractile Mesenteritis, 669.
GERSTER, JOHN C. A.: Retroperitoneal Chyle Cysts with Reference to the Lymphangiomata, 389.
GILMOUR, MONROE T.: Control of Water and Electrolyte Balance in Surgical Patients, 1050.
GINZBURG, LEON: Ileocolostomy with Exclusion, 648.
Gland, Pituitary, Rôle of the, in Water Balance, 1037.
GOLDMAN, LEON: Effect of Distention of Colon and Stimulation of Its Nerve Supply on Flow of Bile from the Liver, 755.

GRAHAM, CHARLES P.: Spinal Extradural Cyst Associated with Kyphosis Dorsalis Juvenilis, 285.
GRAHAM, EVARTS A.: Report on American Board of Surgery, 1115.
GRAHAM, ROSCOE R.: Spinal Anesthesia in Abdominal Surgery, 863.
GRANT, FRANCIS C.: Repair of Cranial Defects by Cranioplasty, 488.
Gravis, Myasthenia, and Tumors of Thymic Region, 544.
GRODINSKY, MANUEL: Retropharyngeal and Lateral Pharyngeal Abscesses, 177.
GROSS, ROBERT E.: Surgical Management of Patent Ductus Arteriosus, 321.
GURD, FRASER B.: Further Experiences in Use of Spinal Anesthesia for Thoracoplasty, 872.

H

Habitual Dislocation of the Digital Extensor Tendons, 81.
HALFORD, F. J.: Sclerosing or Retractile Mesenteritis, 669.
HAMSA, WILLIAM R.: Treatment of Ankle Malunion, 447.
HANFORD, JOHN M.: Aneurysm of External Carotid Artery with Carotid Sinus Reflex, 133; Arteriovenous Aneurysm of the Neck, 131; Cavernous Hemangioma of a Cervical Nerve, 138; Malignant Hemangio-Endothelioma of the Neck, 136.
HARRIS, ROBERT I.: Fat Embolism, 1095.
HART, DERYL: A Discussion of Multiple Neurofibromatosis, 916; Postoperative Temperature Reactions; Reductions Obtained by Sterilizing the Air with Bactericidal Radiant Energy, 291.
HARTMAN, F. W.: Anoxia, 835.
HARVEY, HAROLD D.: Combined Use of Zinc Peroxide and Sulfanilamide in Treatment of Chronic, Undermining, Burrowing Ulcers Due to Micro-aerophilic Hemolytic Streptococcus, 1067.
HAWKES, STUART Z.: Paratyphoid Fever Complicated by Ruptured Appendicitis, 466.
Head Injuries, Revaluation of Treatment of, 357.
HEINBECKER, PETER: Rôle of the Pituitary Gland in Water Balance, 1037.
HELWIG, FERDINAND C.: Liver Trauma and Hepatorenal Syndrome, 682.
Hemangio-Endothelioma of the Neck, Malignant, 136.
Hemangioma, Cavernous, of a Cervical Nerve, 138
Hemolytic Streptococcus, Micro-aerophilic, Chronic Ulcers Due to, Combined Use of Zinc Peroxide and Sulfanilamide in Treatment of, 1067.
Hemorrhage, Massive, in Peptic Ulcer, 376; Shock and Its Differentiation from, 260.
Hepatorenal Syndrome and Liver Trauma, 682.
Hernia Through Transverse Mesocolon and Gastrocolic Omentum, 456.
HICKEN, N. FREDERICK: Effect of Dehydrocholic Acid Upon Biliary Pressure and Its Clinical Application, 67.
HINTON, J. WILLIAM: Massive Hemorrhage in Peptic Ulcer, 376.
HODGE, EDWARD B.: The Samuel D. Gross Prize Notice, 160.
HOLDER, HALL G.: Application of Carbamide (Urea) Therapy in Wound Healing, 94.
HORRAX, GILBERT: Experiences with Total and Intracapsular Extirpation of Acoustic Neuromata, 513.
HORSLEY, J. SHELTON: Peptic Ulcers Perforating into the Pancreas, 606.
HUGGINS, CHARLES: Effect on Bone Marrow of Disruption of Nutrient Artery and Vein, 940.
HUNNER, GUY L.: Congenital Cystic Kidney Treated by Ureteral Drainage, 231.
HUNT, VERNE C.: Lateral Gastroduodenostomy in Cases of Duodenal and Recurring Ulcer, 622.
Hurthle Cell Tumors of the Thyroid, 169.
Hydrocele Sac, Electrosurgical Operation for Excision of an, 314.
Hydrothorax and Ascites, Fibroma of the Ovary with, 731.
Hypertension, Clinical and Experimental Experiences in the Surgical Treatment of Hypertension, 1016.

I

Ileocolostomy with Exclusion, 648.
Influence of Certain Drugs and Anesthetics Upon Gastro-intestinal Tone and Motility, 802.
Inhalation Anesthesia, Trends in, 830.
Injuries, Head, Revaluation of Treatment of, 357.
Internal Biliary Fistulae and Intestinal Obstructions Due to Gallstones, 50; Fixation of Fractures, Use of Vitallium as Material for, 119.
International Cancer Congress, Announcement of Third, 319.
Intestinal Obstruction, Acute, Effect of, on the Blood and Plasma Volumes, 25; The Rôle of the Nervous System in, 411.
Intestinal Obstructions and Internal Biliary Fistulae Due to Gallstones, 50.
Intracapsular and Total Extirpation of Acoustic Neuromata, 513.
Intracranial Arteriovenous Aneurysms, 525; Pressure, Papilledema without, 161.
Intravenous and Regional Anesthesia, 878.
Ischemic Contracture, Volkmann's, Treatment of, 417.
IVY, A. C.: Effect of Distention of Colon and Stimulation of Its Nerve Supply on Flow of Bile from the Liver, 755.

J

JACKSON, REGINALD H.: Technic and Demonstrable Advantages of the Devine Colostomy, 14.
Jaundice, Obstructive, Control of Postoperative Bleeding in, 693.
Jejunum, Rupture of, Evisceration Causing, 464.
JOHNSON, E. K.: Influence of Certain Drugs and Anesthetics Upon Gastrointestinal Tone and Motility, 802.
JONES, RANDOLPH, JR.: Discussion of Multiple Neurofibromatosis, 916.

K

KENT, EDWARD M.: Value of Preliminary Colostomy in Correction of Gastrojejunocolic Fistula, 659.
Kidney, Congenital Cystic, Treated by Ureteral Drainage, 231.
KLEINBERG, SAMUEL: Traumatic Myositis Ossificans, 144.
Knee, Chondritis of, 948.
KOHN, IRVING L.: Significance of Cholesterol Partition of Blood Serum in Surgery of the Gallbladder, 701.
KRUSEN, FRANK H.: Treatment of Volkmann's Ischemic Contracture, 417.
Kyphosis Dorsalis Juvenilis, Spinal Extradural Cyst Associated with, 285.

L

LAHEY, FRANK H.: Carcinoma of the Colon and Rectum, 1.
Lateral Gastroduodenostomy in Cases of Duodenal and Recurring Ulcer, 622; Pharyngeal and Retropharyngeal Abscesses, 177.
LEAMAN, WM. G.: Circulatory Problems of Surgical Importance in Diagnosis of Abdominal Lesions, 766.
Left Subphrenic Abscess, 562.
Leg Length, Equalizing, Clinical Consideration of the Methods of, 992.
LEHMAN, EDWIN P.: Obituary of John Henry Neff, Jr., 153.
Lengthening, Operative, of Tibia and Fibula, 961.
Lesions, Abdominal, Circulatory Problems of Surgical Importance in Diagnosis of, 766.
Lipocaic in Surgery, Significance of, 907.
Liver, Flow of Bile from, Effect of Distention of Colon and Stimulation of Its Nerve Supply on, 755; Trauma and Hepatorenal Syndrome, 682.
LOEB, SAM A.: An Electrosurgical Operation for Excision of an Hydrocele Sac, 314.
LUNDY, JOHN S.: Intravenous and Regional Anesthesia, 878.
Lymphangiomata with Reference to Retroperitoneal Chyle Cysts, 389.
Lymphosarcoma, Primary, of the Stomach, 200.

M

MACGUIRE, CONSTANTINE J.: Adenocarcinoma of the Transverse Colon in a Boy Age Fifteen, 472.
MACKAY, EATON M.: Application of Carbamide (Urea) Therapy in Wound Healing, 94.
MACLACHLIN, ANGUS: Fat Embolism, 1095.
Malignant Hemangio-Endothelioma of the Neck, 136.
Malunion, Treatment of Ankle, 447.
Management, Surgical, of Patent Ductus Arteriosus, 321.
MARTIN, J. D., JR.: Hurthle Cell Tumors of the Thyroid, 169.
MASON, M. F.: Myasthenia Gravis and Tumors of Thymic Region, 544.
Massive Hemorrhage in Peptic Ulcer, 376.
MCCLURE, ROY D.: Anoxia, 835.
MCQUEENEY, ANDREW M.: Internal Biliary Fistulae and Intestinal Obstructions Due to Gallstones, 50.
Mechanical Sphincter, Artificial Anus with, 311.
Medical Treatment of Duodenal Ulcer, Study of Results of, 37.
MEIGS, JOE VINCENT: Fibroma of the Ovary with Ascites and Hydrothorax, 731.
Melanosis Coli, 461.
MELENEY, FRANK L.: Combined Use of Zinc Peroxide and Sulfanilamide in Treatment of Chronic, Undermining, Burrowing Ulcers Due to Micro-aerophilic Hemolytic Streptococcus, 1067.
Mesenteritis, Sclerosing or Retractile, 669.
Mesocolon, Transverse and Gastrocolic Omentum, Hernia Through, 456.
Methods of Equalizing Leg Length, Clinical Consideration of the, 992.
Metrazol for Schizophrenia, Fractures and Dislocations by Muscular Violence Complicating Convulsions Induced by, 107.
MEYERDING, HENRY W.: Treatment of Volkmann's Ischemic Contracture, 417.
MEYERS, RUSSELL: Revaluation of Treatment of Head Injuries, 357
Micro-Aerophilic Hemolytic Streptococcus, Chronic Ulcers Due to, Combined Use of Zinc Peroxide and Sulfanilamide in Treatment of, 1067.
MILLER, EDWIN M.: Bowel Obstruction in New Born, 587.
Minimal Resection of Stomach for Peptic Ulcer, Sympathetic Nerve Block as Adjunct Anesthesia in, 886.
MITCHELL, CHARLES F.: The Samuel D. Gross Prize Notice, 160.
MOCK, HARRY E.: Evisceration Causing Rupture of Jejunum, 464.
MOON, VIRGIL H.: Early Recognition of Shock and Its Differentiation from Hemorrhage, 260.
MORGAN, HUGH J.: Myasthenia Gravis and Tumors of Thymic Region, 544.

Morphine and Cyclopropane Anesthesia, Use of Barbiturates in Preventing Cardiac Irregularities Under Cyclopropane or, 84.
Motility and Tone, Gastro-intestinal, Influence of Certain Drugs and Anesthetics Upon, 802.
Müllerian System in the Female, Unilateral Agenesis of, 316.
Multiple Neurofibromatosis, Discussion of, 916.
Muscular Violence, Fractures and Dislocations by, Complicating Convulsions Induced by Metrazol for Schizophrenia, 107.
Myasthenia Gravis and Tumors of the Thymic Region, 544.
Myeloma of Bone, Solitary, 427.
Myositis Ossificans, Traumatic, 144.

N

National Surgical Societies, Development of, 481.
Neck, Arteriovenous Aneurysm of the, 131; Malignant Hemangio-Endothelioma of the, 136.
Nerve Block, Sympathetic, as Adjunct Anesthesia in Minimal Resection of Stomach for Peptic Ulcer, 886.
Nerve, Cervical, Cavernous Hemangioma of a, 138; Supply on Flow of Bile from the Liver, Effect of Distention of Colon and Stimulation of Its, 755.
Nervous System, Rôle of the, in Acute Intestinal Obstruction, 411.
Neuritis, Optic, 161.
Neurofibromatosis, Discussion of Multiple, 916.
Neuromata, Acoustic, Total and Intracapsular Extirpation of, 513.
New Born, Bowel Obstruction in the, 587.
Newell, E. Dunbar: Gas Gangrene, 100.
Norcross, Nathan C.: Repair of Cranial Defects by Cranioplasty, 488.
Nutrient Artery and Vein, Disruption of, Effect on Bone Marrow of, 940.

O

Obituary: Beer, Edwin, by Ralph Colp, 795; Caulk, John Roberts, by Vilray P. Blair, 151; Fischel, Ellis, by Willard Bartlett, 156; Myles, Sir Thomas, by Donald C. Balfour, 790; Neff, John Henry, Jr., by Edwin P. Lehman, 153; Reder, Francis, by Fred W. Bailey, 149; Rixford, Emmet, by Leo Eloesser, 786; Torek, Franz J. A., by Carl Eggers, 797; Yates, John Lawrence, by Arthur W. Elting, 792.
Obstruction, Acute Intestinal, Effect of, on the Blood and Plasma Volumes, 25; Acute Intestinal, The Rôle of the Nervous System, 411; Bowel, in the New Born, 587; Intestinal, and Internal Biliary Fistulas Due to Gallstones, 50.
Obstructive Jaundice, Control of Postoperative Bleeding in, 693; Origin of Appendicitis in Man, Experimental Proof of, 629.
Omentum, Gastrocolic and Transverse Mesocolon, Hernia Through, 456.
Operation, Complementary and Decompressive, Cecostomy as, 380; for Cure of Flatfoot, 437; Electrosurgical, for Excision of a Hydrocele Sac, 314.
Operative Lengthening of Tibia and Fibula, 961.
Optic Neuritis, 161.
Origin, Obstructive, of Appendicitis in Man, Experimental Proof of, 629.
Orndorff, John R.: Evisceration Causing Rupture of Jejunum, 464.
Orr, Thomas G.: Liver Trauma and Hepatorenal Syndrome, 682.
Ossificans, Myositis, Traumatic, 144.
Ovary, Fibroma of the, with Ascites and Hydrothorax, 731.

P

Pancreas, Peptic Ulcers Perforating into the, 606.
Papilledema without Intracranial Pressure, 161.
Paratyphoid Fever Complicated by Ruptured Appendicitis, 466.
Partition, Cholesterol, of the Blood Serum in Surgery of the Gallbladder, Significance of, 701.
Pasternack, Joseph G.: Solitary Myeloma of Bone, 427.
Patent Ductus Arteriosus, Surgical Management of, 321.
Patients, Surgical, Control of Water and Electrolyte Balance in, 1050.
Pemberton, John deJ.: Correction of article by, 1120.
Peptic Ulcer, Massive Hemorrhage in, 376; Perforating into the Pancreas, 606; Sympathetic Nerve Block as Adjunct Anesthesia in Minimal Resection of Stomach for, 886.
Peritoneum, Primary Closure of, in Acute Appendicitis with Perforation, 222.
Perrett, T. S.: Fat Embolism, 1005.
Pfeiffer, Damon B.: Value of Preliminary Colosotmy in Correction of Gastrojejunocolic Fistula, 659.
Pharyngeal, Lateral and Retropharyngeal Abscesses, 177.
Phemister, Dallas B.: Presidential Address, Development of National Surgical Societies, 481; Valedictory, 960.
Pickhardt, Otto C.: Significance of Cholesterol Partition of Blood Serum in Surgery of the Gallbladder, 701.
Pituitary Gland in Water Balance, Rôle of the, 1037.
Plasma and Blood Volumes, Effect of Acute Intestinal Obstruction on the, 25.
Pneumothorax, Extrapleural, 578.

Poppen, James L.: Experiences with Total and Intracapsular Extirpation of Acoustic Neuromata, 513.
Postoperative Bleeding in Obstructive Jaundice, Control of, 693; Temperature Reactions, 291.
Preliminary Colostomy, Value of, in Correction of Gastrojejunocolic Fistula, 659.
Present Status of Spinal Anesthesia, 851.
Presidential Address, 481.
Pressure, Biliary, and Its Clinical Application, Effect of Dehydrocholic Acid Upon, 67; Intracranial, Papilledema without, 161.
Preston, Robert L.: Review of Operative Orthopedics by, 800.
Primary Carcinoma of the Common Bile Duct, 474; Closure of Peritoneum in Acute Appendicitis with Perforation, 222; Lymphosarcoma of the Stomach, 200.
Problems, Circulatory, of Surgical Importance in the Diagnosis of Abdominal Lesions, 766.
Proof, Experimental, of Obstructive Origin of Appendicitis in Man, 629.
Pulmonary Embolism, Fatal, from Superficial Thrombophlebitis, 1118.

R

Radiant Energy, Bactericidal, Sterilization of Air with, 291.
Rankin, Fred W.: Value of Cecostomy as Complementary and Decompressive Operation, 380.
Reactions, Postoperative Temperature, 291.
Rectum and Colon, Carcinoma of the, 1.
Recurring and Duodenal Ulcer, Lateral Gastroduodenostomy in Cases of, 622.
Regional and Intravenous Anesthesia, 878.
Reichert, F. L.: Sclerosing or Retractile Mesenteritis, 669.
Repair of Cranial Defects by Cranioplasty, 488.
Report on the American Board of Surgery, 1115.
Resection of Stomach for Peptic Ulcer, Minimal, Sympathetic Nerve Block as Adjunct Anesthesia in, 886.
Results of Medical Treatment of Duodenal Ulcer, Study of, 37.
Retractile or Sclerosing Mesenteritis, 669.
Retroperitoneal Chyle Cysts, 389.
Retropharyngeal and Lateral Pharyngeal Abscesses, 177.
Revaluation of Treatment of Head Injuries, 357.
Rienhoff, Wm. F., Jr.: Sympathetic Nerve Block as Adjunct Anesthesia in Minimal Resection of Stomach for Peptic Ulcer, 886.
Riven, S. S.: Myasthenia Gravis and Tumors of Thymic Region, 544.
Robbins, Benjamin H.: Use of Barbiturates in Preventing Cardiac Irregularities Under Cyclopropane or Morphine and Cyclopropane Anesthesia, 84.
Rorertson, James F.: Spinal Extradural Cyst Associated with Kyphosis Dorsalis Juvenilis, 285.
Rodman, J. Stewart: Circulatory Problems of Surgical Importance in Diagnosis of Abdominal Lesions, 766.
Rôle of the Nervous System in Acute Intestinal Obstruction, 411; of the Pituitary Gland in Water Balance, 1037.
Rosenfeld, Louis: The Rôle of the Nervous System in Acute Intestinal Obstruction, 411.
Rourke, G. M.: Control of Postoperative Bleeding in Obstructive Jaundice, 693.
Rupture of Jejunum, Evisceration Causing, 464.
Ruptured Appendicitis, Paratyphoid Fever Complicated by, 466.

S

Sac, Hydrocele, Electrosurgical Operation for Excision of an, 314.
St. John, Fordyce B.: Study of Results of Medical Treatment of Duodenal Ulcer, 37.
Samuel D. Gross Prize Notice, 160.
Saunders, John B. deC. M.: Operative Lengthening of Tibia and Fibula, 961.
Schelling, Victor: Anoxia, 835.
Schnedorf, J. G.: Anoxia, 835.
Schoolfield, Ben L.: An Operation for Cure of Fatfoot, 437.
Sclerosing or Retractile Mesenteritis, 669.
Shelley, Harold J.: Hernia Through Transverse Mesocolon and Gastrocolic Omentum, 456.
Shock and Its Differentiation from Hemorrhage, 260.
Significance of Cholesterol Partition of the Blood Serum in Surgery of the Gallbladder, 701; of Lipocaic in Surgery, 907.
Singleton, Albert O.: Intracranial Arteriovenous Aneurysms, 525.
Sinus Reflex, Aneurysm of External Carotid Aretry with Carotid, 133.
Skin Flaps, Treatment of Avulsed, 951.
Smyth, Calvin M., Jr.: The Samuel D. Gross Prize Notice, 160.
Solitary Myeloma of Bone, 427.
Speed, J. S.: Use of Vitallium as Material for Internal Fixation of Fractures, 119.
Sphincter, Mechanical, Artificial Anus with, 311.
Spinal Anesthesia, in Abdominal Surgery, 863; Present Status of, 851; for Thoracoplasty, Further Experiences in Use of, 872.
Spinal Extradural Cyst Associated with Kyphosis Dorsalis Juvenilis, 285.
Sterilization of Air with Bactericidal Radiant Energy, 291.

STEWART, J. D.: Control of Postoperative Bleeding in Obstructive Jaundice, 693.
Stimulation of Its Nerve Supply on Flow of Bile from the Liver, Effect of Distention of the Colon and, 755.
Stomach, Minimal Resection of, for Peptic Ulcer, Sympathetic Nerve Block as Adjunct Anesthesia in, 886; Primary Lymphosarcoma of the, 200.
Streptococcus, Micro-aerophilic Hemolytic, Chronic Ulcers Due to, Combined Use of Zinc Peroxide and Sulfanilamide in Treatment of, 1067.
Study of Results of Medical Treatment of Duodenal Ulcer, 37.
Subphrenic Abscess, Left, 562.
Sulfanilamide and Zinc Peroxide in Treatment of Chronic, Undermining, Burrowing Ulcers Due to Micro-aerophilic Hemolytic Streptococcus, 1067.
Superficial Thrombophlebitis, Fatal Pulmonary Embolism from, 1118.
Surgery, Abdominal, Spinal Anesthesia in, 863; American Board of, Report on, 1115; of the Gallbladder, Significance of Cholesterol Partition of the Blood Serum in, 701; Significance of Lipocaic in, 907.
Surgical Importance in Diagnosis of Abdominal Lesions, Circulatory Problems of, 766; Management of Patent Ductus Arteriosus, 321; Patients, Control of Water and Electrolyte Balance in, 1050; Societies, National, Development of, 481; Treatment of Hypertension, Clinical and Experimental Experiences in the, 1016.
SUSSMAN, MARCY: Ileocolostomy with Exclusion, 648.
Sympathetic Nerve Block as Adjunct Anesthesia in Minimal Resection of Stomach for Peptic Ulcer, 886.
Syndrome, Hepatorenal, and Liver Trauma, 682.

T

TAYLOR, EARL S.: Primary Lymphosarcoma of the Stomach, 200.
Technic and Demonstrable Advantages of the Devine Colostomy, 14.
Temperature, Postoperative, Reactions, 291.
Tendons, Digital Extensor, Habitual Dislocation of the, 81.
Third International Cancer Congress, Announcement of, 319.
THOMPSON, T. CAMPBELL: Clinical Consideration of the Methods of Equalizing Leg Length, 992.
Thoracoplasty, Spinal Anesthesia for, Further Experiences in Use of, 872.
Thrombophlebitis, Superficial, Fatal Pulmonary Embolism from, 1118.
Thymic Region, Tumors of, and Myasthenia Gravis, 544.
Thyroid, Hurthle Cell Tumors of the, 169.
Tibia and Fibula, Operative Lengthening of, 961.
Tone and Motility, Gastro-intestinal, Influence of Certain Drugs and Anesthetics Upon, 802.
Total and Intracapsular Extirpation of Acoustic Neuromata, 513.
Transverse Colon, Adenocarcinoma of the, in a Boy Age Fifteen, 472; Mesocolon and Gastrocolic Omentum, Hernia through, 456.
Trauma, Liver and Hepatorenal Syndrome, 682.
Traumatic Myositis Ossificans, 144.
Treatment of Ankle Malunion, 447; of Avulsed Skin Flaps, 951; of Head Injuries, Revaluation of, 357; Medical, of Duodenal Ulcer, Study of Results of, 37; Surgical, of Hypertension, Clinical and Experimental Experiences in the, 1016; of Volkmann's Ischemic Contracture, 417.
Trends in Inhalation Anesthesia, 830.
Tumors, of Thymic Region and Myasthenia Gravis, 544; of the Thyroid, Hurthle Cell, 169.
Two Cystic Ducts and Two Cystic Arteries, Double Gallbladder with, 60.

U

Ulcer, Duodenal, and Recurring, Lateral Gastroduodenostomy in Cases of, 622; Study of Results of Medical Treatment of, 37.
Ulcer, Minimal Resection of Stomach for Peptic, Sympathetic Nerve Block as Adjunct Anesthesia in, 886; Peptic, Massive Hemorrhage in, 376; Perforating into the Pancreas, 606.
Undermining, Burrowing, Chronic Ulcers Due to the Micro-aerophilic Hemolytic Streptococcus, Combined Use of Zinc Peroxide and Sulfanilamide in Treatment of, 1067.
Unilateral Agenesis of Müllerian System in the Female, 316.
UPCHURCH, S. E.: Postoperative Temperature Reactions; Reductions Obtained by Sterilizing the Air with Bactericidal Radiant Energy, 291.
Urea (Carbamide Therapy) Application of, in Wound Healing, 94.
Ureteral Drainage, Congenital Cystic Kidney Treated by, 231.
Use of Vitallium as Material for Internal Fixation of Fractures, 119.

V

Valedictory by President, Dallas B. Phemister, 960.
Value of Cecostomy as Complementary and Decompressive Operation, 380; of Preliminary Colostomy in Correction of Gastrojejunocolic Fistula, 659.
Vein and Artery, Nutrient, Disruption of, Effect on Bone Marrow of, 940.
VERMEULEN, C.: Significance of Lipocaic in Surgery, 907.

Vertebral Canal, Dermoid Cysts of the, 273.
VINEBERG, A. M.: Further Experiences in Use of Spinal Anesthesia for Thoracoplasty, 872.
Vitallium, Use of, as Material for Internal Fixation of Fractures, 119.
Volkmann's Ischemic Contracture, Treatment of, 417.
Volumes, Blood and Plasma, Effect of Acute Intestinal Obstruction on the, 25.
Von Recklinghausen's Disease, 916.

W

WANGENSTEEN, OWEN H.: Experimental Proof of Obstructive Origin of Appendicitis in Man, 629.
WARREN, RICHARD: Primary Closure of Peritoneum in Acute Appendicitis with Perforation, 222.
Water Balance, Rôle of the Pituitary Gland in, 1037; and Electrolyte Balance, Control of, in Surgical Patients, 1050.
WAUGH, RICHEY L.: Solitary Myeloma of Bone, 427.
WEEDER, S. DANA: Choledochus Cyst with Double Common Bile Duct, 55.
WHITE, HARVEY L.: Rôle of the Pituitary Gland in Water Balance, 1037.
WIEGE, EUGENE: Effect on Bone Marrow of Disruption of Nutrient Artery and Vein, 940.
WILSON, CLYDE L.: Double Gallbladder with Two Cystic Ducts and Two Cystic Arteries, 60.
WILSON, PHILIP D.: Clinical Consideration of the Methods of Equalizing Leg Length, 992.
WOLFF, WILLIAM A.: Control of Water and Electrolyte Balance in Surgical Patients, 1050.
Wound Healing, Application of Carbamide (Urea) Therapy in, 94.
WRIGHT, LOUIS T.: An Electrosurgical Operation for Excision of an Hydrocele Sac, 314.

Z

ZIEROLD, ARTHUR A.: Gangrene of the Extremity in the Diabetic, 723.
Zinc Peroxide and Sulfanilamide in Treatment of Chronic, Undermining, Burrowing Ulcers Due to Micro-aerophilic Hemolytic Streptococcus, 1067.

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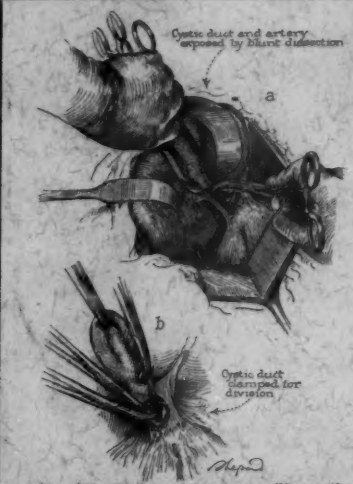

Fig. 232. Cholecystectomy. (a) The cystic duct and cystic artery are being dissected free from the tissues of the duodenal-hepatic ligament with the tip of a Moynihan forceps; (b) the cystic duct is doubly clamped with Moynihan forceps. (Illustration reduced from original.)

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